DOCTOR OF PHILOSOPHY

The effect of deprivation and comorbidity on survival in patients with head and neck cancer

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THE EFFECT OF DEPRIVATION AND COMORBIDITY ON SURVIVAL IN PATIENTS WITH HEAD AND NECK CANCER

A dissertation presented for the degree of Doctorate of Philosophy at the University of Dundee

by

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Makachiya E, Ogston S, Sullivan FM, Wells EM, McCowan C. The impact of comorbidity and socioeconomic status on mortality in Head & Neck cancer: A systematic review. PLoSOne, 2015; In press.

Makachiya E, McCowan C. Developing of a tool for the quality assessment of survival studies in systematic reviews. BMC Methodology, 2015; In press.

Conference Presentations

Society for Academic Primary Care (SAPC) Conference 2012 Poster Presentation entitled: The influence of socioeconomic status and comorbidity in head and neck cancer survival: A systematic review

MRC (Medical Research Council) Student Retreat 2013 Poster Presentation entitled: The relationship between comorbidity, socioeconomic status and mortality in patients with head & neck cancer in Tayside and Fife

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Isaiah 12: 2 Behold, God is my salvation; I will trust, and not be afraid: for the **LORD JEHOVAH** is my strength and my song; he also is become my salvation.

DECLARATION

I declare that this thesis has been composed by me and that the research it describes has been done by me. This thesis has not been accepted in any previous application for a degree. All quotations have been distinguished by quotation marks and the sources of information clearly acknowledged.

Signature _____

Date

_____

I certify that Elsie Hazvinei Makachiya has completed the equivalent of nine terms of experimental research and that she has fulfilled the conditions of the relevant Ordinance and Regulations of the University of Dundee, so that she is qualified to submit this thesis in application for the degree of Doctor of Philosophy.

Signature _____

Date

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ABSTRACT

Introduction

Research suggests that patients with head and neck cancer from poorer backgrounds are more likely to have recurrences or die earlier than similar patients from affluent backgrounds. Survival is influenced by tumour characteristics on presentation and a range of individual factors such as socioeconomic status and comorbidity. Deprived patients of more advanced age have a higher likelihood of having comorbidity; this may be due to high-risk lifestyle behaviours such as smoking and drinking. Therefore, it seems reasonable to assume that survival will be lower in these deprived patients which can be attributed to comorbidity compared to index diseases such as the head and neck cancer itself.

Survival rates for head and neck cancer patients are approximately 50% in the first five years in Scotland. This is dependent on a range of individual and tumour-related factors such as head and neck cancer sub-type and stage at diagnosis. The risk of head and neck cancer developing in deprived patients has been likened to that of developing head and neck cancer in heavy smokers. While the relationship between deprivation and comorbidity in head and neck cancer has been established, how both factors affect survival is yet to be explored. Reviewing these two factors individually has demonstrated the need to assess how both interact with each other in determining clinical presentation and survival.

Aim

The aims of this thesis are:-

- To investigate the roles and interrelationship between comorbidity and deprivation on the survival of HNC patients.

- To investigate whether there are differences in HNC presentation based on comorbidity and deprivation.
- To ascertain whether patients from deprived backgrounds with comorbidity present with more advanced cancers.

Methods

In order to answer the research questions, this project began by describing the index disease, HNC and how comorbidity and deprivation are placed within the epidemiology of this disease using systematic review methods. The rationale for embarking upon this study was highlighted.

Data linkage of administrative datasets

We used anonymised patient data that was accessed through an encrypted repository held by the Health Informatics Centre. The data that was used in the retrospective cohort analysis was obtained from a prospective dataset collected by the Fife Head and Neck cancer Specialist Nurse (Fife data) and a retrospective case note review from the Tayside oncology records held by the Ear Nose and Throat Department and the Oral and Maxillofacial Surgery team. Thereafter we matched the patient data with that from routine medical datasets such the Scottish Morbidity Records, SMR01- inpatient discharges and SMR06 – Cancer Registry data. We conducted survival analysis methods with the intent of assessing the impact of both comorbidity and deprivation in determining survival.

Results

The systematic review found that worsening levels of comorbidity were linked to reduced survival whereas patients with low incomes and poor educational attainment also had poor survival outcomes. Being young and having severe comorbidity appeared to also be associated with poorer survival. In the retrospective cohort analysis, the level of association between risk of

death with comorbidity and deprivation could not be clearly ascertained in the patients from Fife. The Tayside data to a larger extent supported the systematic review findings particularly for the comorbidity measures with clearly defined measures of association for the Scottish Index of Multiple Deprivation income and education domains.

Conclusions

This thesis was able to use evidence triangulation by way of a systematic review of the literature followed by a retrospective cohort analysis to investigate what influence on prognosis both comorbidity and deprivation posed in patients with head and neck cancer. There was substantiation of both factors interacting with head and neck cancer to cause a significantly reduced impact on survival. The inherent difficulties of measuring socioeconomic status and comorbidity encountered in this thesis may go some way towards illustrating the complexity and multifaceted nature of both comorbidity and socioeconomic status; particularly the quite complex interplay between socioeconomic status, comorbidity, stage at diagnosis, and access to care in head and neck cancer, and these factors' ultimate impact on survival.

We found that socioeconomic status i.e. deprivation, comorbidity, stage at diagnosis, access to care, and survival are all potentially causally related. Future work directed at using administrative data linked to medical records would not be sufficient; there is need for epidemiological and clinical studies to unravel the survival disadvantage. To this end clinical cohorts could be nested within larger registry based studies which would allow for uniform interventions based on clinical practice guidelines, uniform SES measurement and ascertainment of comorbidity using a head and neck cancer comorbidity index, i.e. the Washington University Head and Neck Cancer Index.

Chapter 1

1.1. Head and Neck Cancer: An Introduction

1.1.1 Chapter Outline

This chapter will give the reader the background to the problem of head and neck cancer (HNC) in the population. HNC is a term used to define a distinct group of cancers occurring within the head and neck region. The statistics from the UK and globally show an unequal survival burden in people from deprived backgrounds compared to those from affluent backgrounds. Another important determinant of HNC presentation and survival that will be discussed is the issue of comorbidity.

The relationship between HNC incidence and survival based on comorbidity and socioeconomic status (SES) will be explained. HNC is a disease mainly diagnosed in the elderly, and as comorbidities occur more frequently in older people hence it is expected that with advancing age comes the increased chance of an elderly person having some concurrent chronic medical conditions.

Comorbidity refers to a chronic illness that occurs alongside and usually independent of the disease under study (1), in this case HNC. It is apparent that having one or more of these pre-existing diseases may affect the severity of the cancer thereby reducing the likelihood of a favourable outcome. In the case of SES, HNC is normally associated with chronic exposures such as high smoking rates and excess alcohol consumption, with both risk factors noted to have higher prevalence in low SES (deprived) groups which may explain the higher HNC incidence in this group. Therefore HNC is compounded by comorbidity and the social patterning of this disease predominantly in deprived groups requires further exploration. The chapter will outline

the focus and aims of the project. It will also provide definitions of what is and is not included within the definitions of SES and comorbidity. This chapter will also provide the reader with an understanding of why the subject was chosen and considered important enough to merit this thesis.

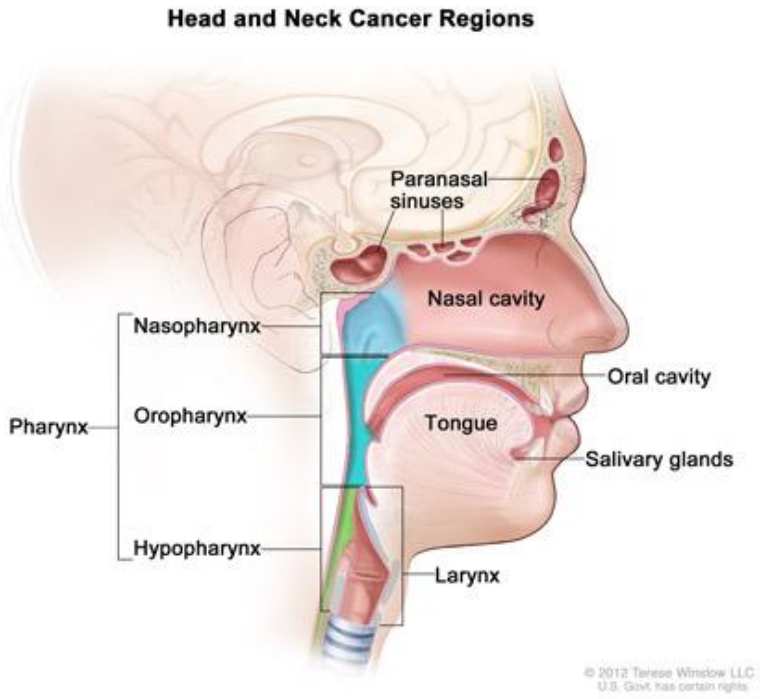
1.2. Head and neck cancer

HNC is the collective term that defines neoplasms (cancerous tumours) that derive from a distinct group of primary sites within the head and neck area. (2, 3) There are more than 50 epidemiological and clinical disease entities within the head and neck area and as there are more than 30 different sites within the head and neck where this form of cancer can develop, it is important to understand the exact anatomic location of these sites as depicted in Figure 1 below.

- the pharynx, with its three component parts namely: nasopharynx, hypopharynx and oropharynx; larynx;
- lip and oral cavity i.e. gum, tongue, floor of mouth, hard palate;
- paranasal sinuses and nasal cavity;
- and the salivary glands. (4, 5)

There are more than 50 epidemiological and clinical disease entities within the head and neck area and as there are more than 30 different sites within the head and neck where this form of cancer can develop, it is important to understand the exact anatomic location of these sites as depicted in Figure 1 below.

Figure 1 HNC sites



Source: National Cancer Institute (6)

As a result of the possible misinterpretation of HNC due to case mix differences, this report will use the following ICD-10 codes to refer to HNC, Codes C00.0 to C32.9. (7) It is important to note that cancers that occur within the thyroid, brain, ear or eye are not included in the definition of HNC used in this thesis. Most HNCs (90%) are carcinomas, in particular squamous cell carcinomas as most types of HNC occur in epithelial tissue. (8)

Incidence of HNC increases with age with the majority of cases in Europe occurring in those aged over 50 years, (9) as people who live longer are more likely to develop HNC. (10) With the global projections of an increase in the elderly population due to increased life expectancy, this will become an increasing problem for Scotland as HNC services will experience the effects of this demographic shift. Smoking cessation has had an impact on incidence however human papilloma virus positive (HPV+) cancers are on the rise especially in the younger population. (11) An ageing population represents an increase in comorbidities as these occur more frequently in the elderly.

Age introduces the probability of an excess burden of disease therefore it is necessary to factor comorbidity status into therapeutic interventions to minimise adverse treatment effects such as drug interactions or polypharmacy, (12-14) and additionally, increasing comorbidity has also been associated with a higher incidence of postoperative complications. (15) Incidentally HNC treatments are noted to be invasive which introduces an elevated risk of post procedural complications which also amplifies the risk of death. Careful planning and clinical decision making may not eradicate the risks posed by drug interactions and may have a detrimental effect on the survival of the patient. It remains unclear whether the elderly benefit from these invasive interventions or whether treatment selection based on patient factors favours better outcomes.(15-18)

1.2.2. HNC Incidence

HNC is the 6th most common site of cancer in the world (19-21) and has been found to be the 6th leading cause of cancer deaths globally. (19) It is listed as the 10th most commonly occurring cancer in Scotland (Table 1).

Table 1 HNC incidence in Scotland

HNC (C00-C14, C30-C32)	Number	10 year change	P value
All persons	1 278	+11.5%	P<0.0001
Males	869	+6.8%	P=0.0628
Females	409	+25.4%	P=0.0001

Source: ISD Scotland (22)

In 2010, 3% of all malignancies within the UK were attributed to cancer of the head and neck, with the majority of cases being recorded in people aged 50 and over.(23) The most common site for HNC in the UK is the mouth i.e. oral cavity, with evidence of site specific cancers having different rates, e.g. laryngeal cancer accounts for 2400 cases per year), nasal cavity and paranasal sinus

cancer 440 cases, while nasopharyngeal and salivary gland cancers are very rare forms of HNC. The sex ratio of males to females has decreased from 5:1, 50 years ago to 2:1, with males bearing the larger burden of disease. Although incidence of this form of cancer increases with age, MacFarlane *et al* found a high incidence of cancer of the tongue in young Scottish males in the late 1980s. (24)

Global incidence rates are increasing; in the UK this equates to approximately 8000 cases per year. Approximately 90% of cases arise in over 50s with male to female ratio for oral cavity and laryngeal cancer at 2:1 and 5:1 respectively. (25) The incident cases for Scotland are approximately 1000 each year which are the highest rates for HNC within the UK. (26) There is compelling epidemiological evidence of HNC increasing with age but there is an emerging trend of younger people being increasingly diagnosed with this oropharyngeal cancers, with clear evidence that these cases are linked to the human papillomavirus (HPV). (27) HPV-related HNCs have important clinical and prognostic differences compared to those typically associated with tobacco and alcohol use. (28-32)

1.2.3. Risk factors

The chronic exposures of tobacco (smoking) and alcohol are the most important risk factors for HNC especially for oral cavity, oropharynx, hypopharynx and larynx cancer subtypes accounting for approximately 75% of these cancers.(33) These two risk factors are known to have a multiplicative effect dependent on the level of consumption and especially more so in the presence of poor oral hygiene. (34) This multiplicative causal association has been estimated to increase risk to as high as over 35 times in heavy smokers who drink heavily when compared to those that neither smoke nor drink.(33, 35) More recent risk modelling has placed the risk of tobacco smoking alone to between 3 and 9-fold while both tobacco and alcohol have been predicted to increase risk by up to 100-fold. (36) According to findings from the National Cancer

Institute, 85% of HNCs are attributable to tobacco use, while others have placed this estimate to be as much as 90%.(6, 25) A common aspect is that the amount smoked has a reciprocal elevation to risk of developing HNC i.e. previous research has noted that the dose response relationship increases from 5 to 25 fold when comparing smokers to non-smokers. (37, 38) In addition, pipe or cigar smoking have been found to greatly elevate the risk of developing this cancer.(39)

Chewing tobacco and betel nut has also been indicated in the causal pathway as both substances have carcinogenic properties. Studies of incidence of oral cancers in the UK show a higher HNC incidence in Chinese and South Asians which has been attributed to prevalence of betel liquid and areca nut chewing. (40, 41) Cannabis was also implicated in the aetiology of HNC (42) but there is little evidence of this with only one other research paper identifying a statistically significant causal relationship despite cannabis having similar carcinogenic properties to tobacco.(43) The International Agency for Research on Cancer (IARC) conducted a review of the link between cannabis and oral cancers and did not find a causal link, however cannabis use and the number of oral sexual partners as causal factors are being explored further.(44, 45) Socioeconomic differences in lifestyle also contribute to the incidence of HNC e.g. a diet low in fruit and vegetables has been identified as a risk factor for HNC, as it has been found that such a diet is usually associated with patients from deprived backgrounds who have excessive alcohol and heavy smoking habits which in turn increases the risk of HNC. (46, 47)

There is evidence that demonstrates that HNC occurs in people who never smoked nor drank, with 20% of cases falling into this category. (48) These cases are attributed to HIV, HPV, Plummer-Vinson syndrome or Paterson-Brown Kelly syndrome in the United Kingdom, Epstein-Barr virus, occupational exposure, poor oral hygiene, immune-suppression from post-transplant therapy and Fanconi anaemia. (6, 49)

There has been a notable shift in the epidemiology of HNC due to an association between human papillomavirus (HPV) and HNC. (27, 50-52) Approximately 25% (53) of HNC cases are caused by

HPV with the majority of these cases arising in the oropharynx. 85% of HNCs are caused by tobacco use while alcohol increases the risk, while 50% of oropharyngeal cancers are due to HPV positivity. In the last 20 years there has been a clear increase in HPV+ HNC with the predominant subsite being the oropharynx. (54, 55) (55, 56) (57) The risk profile of the HPV+ HNC patient is that of a younger adult with limited or no heavy smoking or drinking habits which is an atypical presentation to that of an elderly male, heavy smoker and drinker.(58) The strains that have been implicated in HPV-positive HNC are types 8, 16, 33 and 35 with up to 90% of HPV-positive HNC being caused by type 16. The most important risk factor is the total number of lifetime sexual partners particularly oral sex partners. An interesting fact is that when comparing cancers of the head and neck is that the HPV -positive cases have better outcomes.(27, 42, 59-63) Research has found that, HPV-positive cancers have an 85% to 90% disease-free survival rate over five years. (64)This has been put down to the better responses to chemo-radiation, but the exact mechanism that accords better prognosis is not fully understood and requires further investigation.(52, 65-69) Scheich speculated that improved outcomes may be due to DNA variations between HPV-positive and HPV-negative cancers which make HPV-positive tumours more favourable to treatment.(27) Poor prognosis in HPV-negative HNC incident cases may be due to late presentation with metastatic disease apportioning the poor five-year survival rates of approximately 40-50%.

1.2.4. Diagnosis and Symptoms

HNC signs and symptoms are usually picked up by a dentist during a routine dental check-up or when the patient visits their GP with a specific complaint. It is common that symptoms do not automatically indicate cancer but vary from, difficulty or pain when chewing or swallowing, trouble with speaking or breathing, a non-healing mouth ulcer, persistent throat or ear pain, a swelling or lump in the mouth or neck. Less commonly there may be unexplained changes in the lining of the mouth or on the tongue, which can be white patches (leukoplakia) or red patches

(erythroplakia) – these are usually painless but can sometimes be sore and may bleed. (5) The symptoms of HNC are especially insidious as they are similar to the symptoms of minor ailments which may explain why early diagnosis may be missed due to this clinical manifestation. Once HNC is suspected, the patient is usually referred to a local hospital where their case is reviewed by either an Oral/Maxillofacial surgeon or alternatively the Ear Nose and throat (ENT) specialist, an otolaryngologist and diagnosed.

1.2.5. Prognosis

The prognosis for HNC varies greatly by TNM stage at diagnosis, i.e. size of the tumour, extent of lymph node involvement and the presence /absence of metastatic disease. The actual site and nodal status are also important determinants of outcome. All these disease characteristics have a significant role in establishing survival but nodal status is vital as nodal disease is associated with poor prognosis. 5 year survival rates for HNC are between 60% and 90% in the UK and figures for median survival are less than 3 months for advanced disease without treatment while the Scottish Cancer Intelligence Unit, found that relative survival; was poorest among the most deprived areas. (4, 70)

There appears to be an association between where one lives and survival following a diagnosis of cancer, also known as the "postcode lottery of care" which states that depending on where an individual lives, determines what treatment that individual gets and whether that individual subsequently survives. It was noted in the 1990s, that regional variations existed for cancer survival but the exact reasons for this variation were unclear, although the clinical course of the disease could explain some of these differences. (71) The typical HNC patient as defined by Hall *et al* (58) can unwittingly reduce long term survival prospects based on that individual's personal characteristics:

- Being male aged 65+,
- being deprived,
- previous occupational exposure, e.g. exposure to dust, chemicals, fumes etc.'
- have a history of excess smoking and alcohol intake,
- have low awareness of severity of symptoms,
- presenting with an advanced tumour (s).

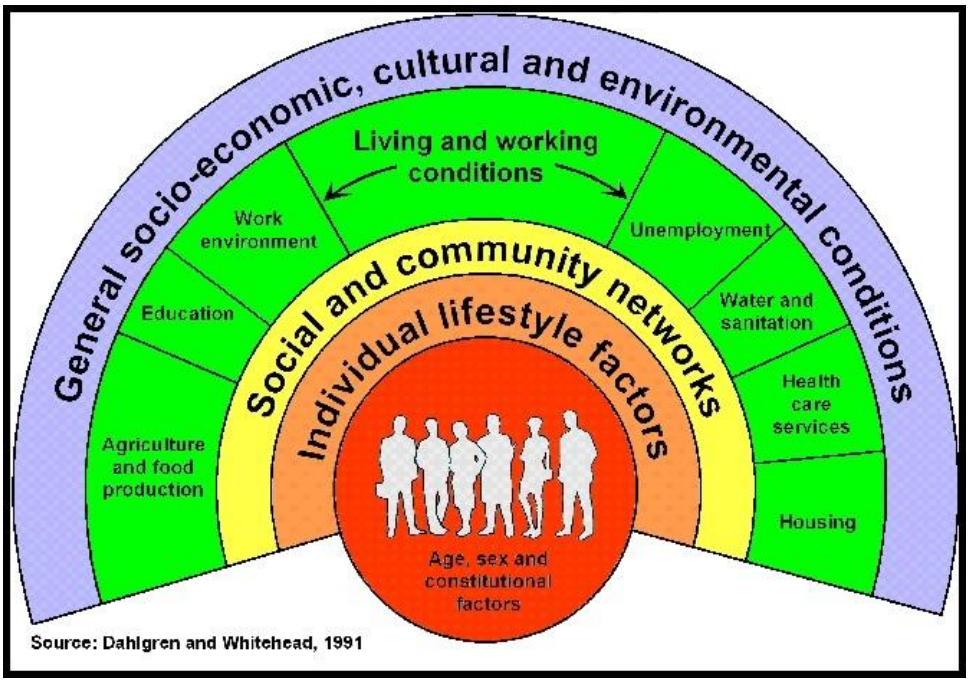
This clustering of disadvantage makes it less likely for the typical patient to have a good prognosis especially as males are considered as hard to reach due their poor help-seeking behaviours (72). As evidenced by Hart *et al* (73), poor people are more likely to die from cancer compared to the rich, while Bungay (74), found that patients of similar socio-demographic backgrounds to the typical head and neck patient were likely to have more aggressive cancers due to poor diet and risky lifestyle behaviours.

1.2.6. Determinants of HNC prognosis

In HNC cases the outcomes for individual patients are also determined by the presence of comorbidities, while late presentation equates to more extensive treatments that result in significant disease burden and less positive outcomes.(46) Although treatments aim to eradicate the disease while maintaining function, there may be various physiological changes to structures that were affected by the cancer and the multitude of treatment modalities used. This can result in a loss of the ability to speak, swallow, and eat, breath, and work and comfortably carry out social interactions. Although the cancer may be gone, the loss of basic functioning abilities to communicate has a profound psychological impact on the patient. It is common for these patients to feel lonely and unable to communicate effectively with family and/or peers and can end up with a diagnosis of depression. Most individuals lose their livelihoods and all these factors contribute greatly to diminishing that individual's quality of life. Logeman (75) recommended a

holistic care approach to the treatment and after care of HNC patients, taking into account other factors such as the social, lifestyle and environmental influences which encompasses theories such as the determinants of health model (Figure 2). (76)

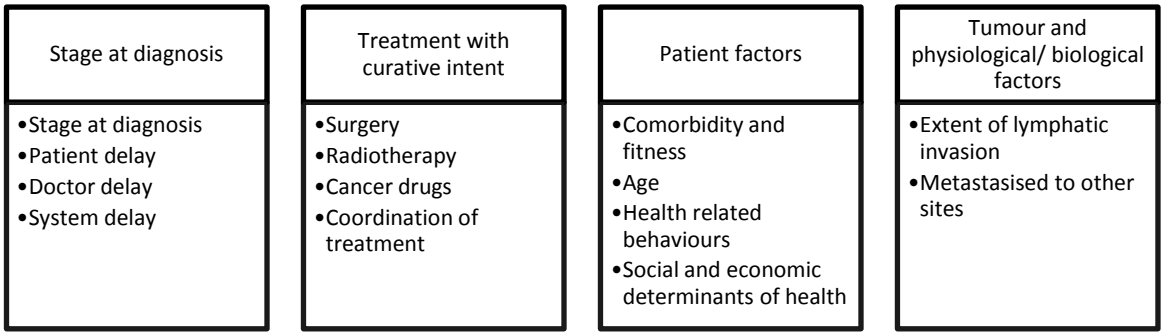
Figure 2 Determinants of health



Source Dahlgren and Whitehead (76)

On the age spectrum, although mortality has decreased in those aged 75 years and under, the same cannot be said for the older HNC patients. (77-80) It appears that oncologists are reluctant to offer more invasive treatments. These inequalities in therapeutic intervention choices pose serious challenges to the effective reduction of mortality. Foot and Harrison identified four key categories of cancer survival determinants which are equally applicable to HNC (Figure 3).

Figure 3 Possible drivers for international variation in cancer survival



Adapted from Foot and Harrison (81)

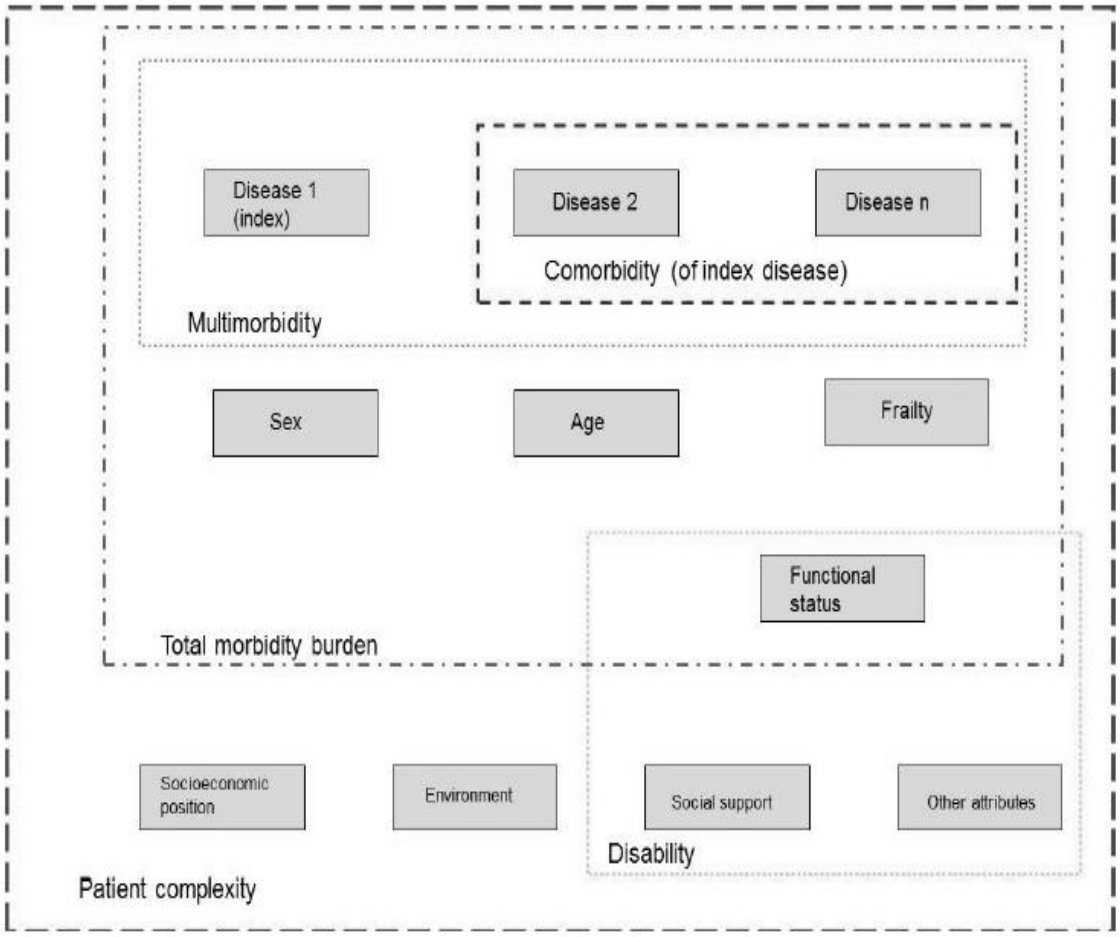
The aetiology of HNC makes comorbidity common and as the typical patient is elderly this makes the presence of concurrent chronic conditions more numerous. As highlighted by Boeje *et al* (11) the changing world demographics mean more diagnoses of HNC will occur with more patients having comorbidities which means comorbidity status has an importance in relation to prognostication. As elderly patients are not included in clinical trials, the changes in life expectancy patterns means further study of the impact of comorbidity on survival is required to assess whether comorbidity accords greater survival disadvantage HNC patients.

1.3. Comorbidity Status

The term comorbidity was introduced to medicine by Feinstein to denote those cases in which, "a distinct additional clinical entity," occurred during the clinical course of a patient having an index disease. (1) Medical Subject Headings (MeSH) defines comorbidity as a complication i.e. a condition that existed prior to the index disease ensues. From this definition it appears as though the sequence by which comorbidities appear may have important connotations for the prognosis of HNC as the index disease. Comorbidity is useful in clarifying the total burden of disease and the

implications of the comorbidity on the individual(82) but it is not to be mistaken for other constructs of coexistent disease as depicted in Figure 4.

Figure 4 Constructs of comorbidity



Source: Adapted from Valderas *et al* (82) by Safarti (83)

As described by Sarfati, "this diagram shows the close relationship between *comorbidity* and *multimorbidity*, with the difference being that comorbidity is measured in relation to a primary index disease, whilst multimorbidity is a total measure of all diseases occurring concurrently in an individual". (83) It is important to clarify the difference between comorbidity and multimorbidity as they have been considered as meaning the same thing. Comorbidity refers to the presence of condition(s) or disease that precedes the index/primary disease that is under study. Multimorbidity differs as it is an aggregation of the index disease and any concurrent medical

conditions i.e. comorbidities. The two terms are interrelated because one cannot exist without the other as comorbidity is an additional clinical entity that arises in the presence of a primary disease. The total disease burden of the comorbidity alongside the primary disease results in multimorbidity. In this thesis we did not look at multimorbidity as it was not a prognostic factor that we sought to investigate. In this model it is clear that patient complexity is compounded by other factors within the patient's environment such as socioeconomic position, i.e. SES.

As the natural course of the disease and its corresponding intervention(s) can influence the course of the second or even third disease, comorbidity has a direct impact on the single disease approaches of conventional oncology. Within this thesis HNC is the index disease as it is the disease that has prompted the episode of care under study while comorbidity will be defined as a disease(s) that:

a) occurred prior to the cancer, and
b) occurred as a result of the cancer treatment.

Comorbidity in cancer is the presence of one or more medical ailments occurring concurrently alongside the primary tumour. This comorbidity has the potential to significantly affect prognosis in HNC patients, and is contributed to by tobacco, and alcohol misuse which are significant aetiological agents in HNC carcinogenesis. There is a pathophysiological explanation for comorbidity; it is a natural process in the natural course of a disease, e.g. diabetes mellitus and cardiovascular disease. (84) It is essential to highlight that comorbidity is not a complication in this instance that occurs as a side effect of cancer treatment. Instead it is a pre-existing or secondary disease that is entirely independent of the cancer (index disease) diagnosis.

Comorbidity should not be confused with multi-morbidity which is the total sum of the existence of two or more pre-existing medical conditions in a patient without the specification of an index disease as depicted in Figure 4. It is known that as the risk factors for HNC are similar to those

causing pulmonary, respiratory and hepatic disease, hence it is highly likely that a HNC patient will have a condition that pre-exists HNC.

Also as already established, cancer occurs more commonly in advanced ages, hence it is likely that these patients will have an underlying illness (comorbidity) as chronological age is not always a good indicator of health status. However there is risk of unintentional bias here, a phenomenon known as the Berkson's fallacy, as disease clusters are more likely in health seeking patients than in the general population. (85) Therefore patients that are under medical care for a chronic disease are more likely to get a diagnosis of other diseases than people who do not receive such care. Comorbidity poses significant implications to the management of cancer patients as it may cause these patients to be more prone to acute illness episodes with high likelihood of presenting an atypical clinical picture to the responsible health professionals. (86)

1.3.1. Comorbidity measurement

It is unclear how to consistently measure the existence of comorbidity in cancer patients and evaluate its impact on survival, but some measures for aggregating comorbid disease have been developed. The two types of comorbidity indices defined by Hall (87) rely on:

1. Primary data collected by physicians or nurses or through medical record review
2. Secondary data that is derived from healthcare databases

Comorbidity was brought to the fore in cancer prognosis research to investigate the benefits of modifications to treatment approaches in light of the presence of comorbidity.(88) To gain a fuller understanding of how comorbidity affects and contributes to a cancer patient's burden of disease, it is necessary to use a measure of the comorbidity, to allow assessment of a patient's combined burden of illness. Using these indices in cancer research gives a clear illustration of the prognostic implications of comorbidity. The most widely used comorbidity assessment tools have been condensed into Table 2 as highlighted by Paleri and colleagues (89) although the Adult

Comorbidity Evaluation 27 (ACE 27) and the Charlson Index are the most commonly used indices to quantify comorbidity within HNC oncology.

Table 2 Comorbidity indices

INDEX NAME	INDEX CHARACTERISTICS
Adult Comorbidity Evaluation 27 (ACE 27)	Includes 27 different comorbid ailments from different organ systems Each ailment graded into a three-category severity system (mild, moderate, severe) Overall comorbidity score assigned according to the highest single scoring ailment, except when two or more grade 2 ailments are present. In this situation, the score is designated grade 3
Charlson Comorbidity index (CCI)	Developed from a study of causes of 1-year mortality in a cohort of 559 patients. Validated on a further sample of 685 patients A weighted index with 19 comorbid conditions that take into account the number and the seriousness of comorbid disease Classifies patients into four grades based on comorbid disease
Elixhauser Comorbidity Index (ECI)	Developed using administrative data from a state-wide California inpatient database It is a list of 30 comorbidities relying on the ICD-9-CM coding manual that are significantly associated with in-hospital mortality and includes both acute and chronic conditions
Head and Neck Cancer (HNCA) Index	Refinement of the CI by selecting and weighting prevalent comorbid conditions in the HNC population A weighted index with eight comorbid conditions An adjusted relative risk for each condition used as a weight
Alcohol–Tobacco-Related Comorbidities Index (ATC)	Simple count of 11 conditions that are related to alcohol and tobacco consumption with no weighting Range of scores from 0 to 11
National Cancer Institute (NCI) Comorbidity Index	Comorbid conditions selected according to the leading cause of chronic disease present in the population 24 Comorbidities, score calculated by summing all conditions present Two levels of comorbidity burden assigned based on scores
Washington University Head and Neck Comorbidity Index (WUHNCI)	Summative scale with a list of seven weighted items Comorbidity score calculated as the sum of weights of each of the comorbidities present Validated on colon cancer population

Source: Adapted from Paleri *et al* (89)

Oncologists are faced with patients with multiple health and social care needs and ignoring these factors may have detrimental effects on prognosis. Unfortunately prescribing guidelines do not always cater for complex patient related factors such as comorbidity and there is a paucity of evidence indicating how polypharmacy affects elderly cancer patients. Older patients have a disproportionate burden of disease and this depicted clearly by the rates of HNC incidence in the elderly compared to younger age groups. These rates show that HNC cancer is more common in people aged 50 years and older, which corresponds with Extermann's assertion that, "time to accumulate mutations and epigenetic modifications, oxidative damage, modifications of the immune system and decreased cell repair mechanisms have all been hypothesized." (90)

One could argue that screening is the cause of this artefact but as screening is only provided in colorectal, breast and cervical cancers, this does not explain these findings. Therefore the opinion that cancer occurs more frequently as one gets older is accurate. Despite the existence of known oncologic treatment regimens for HNC; these have to be tailored to each individual patient as pre-existing medical conditions have to be factored into the therapeutic approach. Comorbidity can be defined as a serious medical condition that is not linked to primary disease under study but affects a major organ system such metabolic or cardiovascular. (91)

Of interest when reviewing comorbidity in cancer patients is the comorbidity that precedes the diagnosis of cancer. This is of more importance as cancer treatment regimens have to be adjusted for the pre-existing chronic illness due to the risk of polypharmacy. (12-14, 92) Polypharmacy has been defined as the practice of over prescribing or duplicating similar drug types to the same patient. (12) This is a very likely scenario in HNC care as the majority of patients are elderly and likely to have concurrent health problems; this is the reason they have more prescriptions per head than any other group. (13) It is noteworthy that as comorbidities usually precede HNC by between five and 15 years, the challenge of polypharmacy is inherently complex. (93)

Oncologists face the test of attempting to treat a cancer in the presence of a comorbidity while navigating the risk of medicines interacting and causing more harm to the patient. These possible interactions can cause further morbidity through pharmacokinetics as this process is impaired in the aged due to age related factors such as delayed stomach emptying and reduced body fat ratio. Reduction in body mass index is particularly important in HNC as the effects of treatment can cause dramatic weight loss thereby affecting pharmacokinetics. Aging is also affected by pharmacodynamics (what a drug does to a body) through side effects of the drug, medicine toxicity and potential drug interactions which may cause iatrogenesis, site of action and response of the body to drugs. Drugs to treat comorbid disease may have implications on how cancer is treated and probability of disease recurrence. (11, 94-96)

An essential aspect of personalised medicine involves developing an understanding of how host attributes such as age, sex and comorbidity status can affect cancer biology, treatment tolerance and efficacy. Holistic assessment of physiological functioning as an essential aspect of oncology has been poorly researched as older cancer patients are underrepresented in clinical trials. (97) Therefore it is unclear how being older and having comorbidity affects drug interactions and resultantly treatment outcomes. Comorbid illness and its treatment may interact with cancer treatment approaches therefore health related quality of life is important in determining survival. (90)

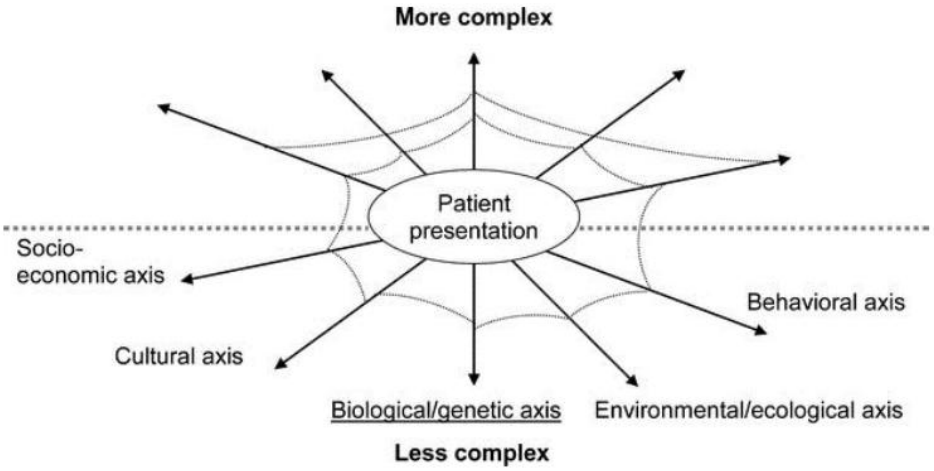
Among HNC patients finding complex patients is a common phenomenon as the age (being elderly) and having comorbidity makes it more challenging. (98) Other environmental and social factors are known attributes that contribute to this complexity. This makes clinical decision making and resultant treatment plans remarkably complicated. Current clinical practice guidelines do not take comorbidity into account. As described by Sarfati (83) much of the research and planning relating to cancer and cancer care assumes a single disease paradigm despite overwhelming evidence that comorbidity affects treatments, increases hospital

admissions, reduces quality of life and raises the risk of death, '[a]lthough patients with more than one diagnosed disease are frequently encountered in modern medical practice, the inter-relationships and effects of multiple diseases have not received suitable taxonomic attention in clinical science." (1) Despite this being pointed out all those years ago, comorbidity is considered more as a confounder in most primary research papers rather than a prognostic factor in its own right alongside other factors such as age, sex, and SES. Notwithstanding this approach of treating comorbidity as a confounder, some researchers have identified its prognostic importance which has led to the development of clinically-based comorbidity indices to assess the role of comorbidity in outcomes for patients.

The Charlson Comorbidity Index (CCI) (99) although widely used has some limitations. It was developed in 1987 which may account for the reason why it focuses on some conditions that do not have a direct impact on survival. Also some conditions such as AIDS are rarely encountered as patients can live with HIV for decades without developing AIDS. It does not consider the relative importance of a multiplicative effect of multiple conditions but instead treats all conditions as having an additive impact on survival. (100) The National Institute on Aging (NIA) Geriatrics and Clinical Gerontology Program (101) convened a taskforce on comorbidity which determined that there was no single measure that could ascertain comorbidity adequately. In her review of comorbidity instruments, Sarfati (102) found that there was no gold standard for risk adjustment of comorbidity.

An alternative method is the systems approach that depends on models involving varying numbers of individual conditions such as the Elixhauser comorbidity index (ECI) developed by Elixhauser *et al* (103) in 1998. Valderas *et al* (82) in their review of comorbidity highlighted patient complexity (98, 104);which encompasses all the health determinants (Figure 5). Complexity has the potential to expand the idea of comorbidity further by considering the influence of all these other factors which may influence patient outcomes.

Figure 5 Patient complexity



As described by Sarfati (105), "the concept of complexity reflects the intricate interactions between a multitude of factors that impact on care and outcomes at the individual level". Comorbidity is common, particularly in the older population and HNC is a disease that occurs commonly in older people, hence the unravelling of the prognostic impact of comorbidity is of importance.

Despite awareness of the challenge posed by comorbidity, not enough is being done to address this issue in all cancer patients and particularly in this case; HNC patients. There is currently no widely accepted conceptualisation that portrays the numerous influences that together make a patient complex.

1.4 Socioeconomic status (SES)

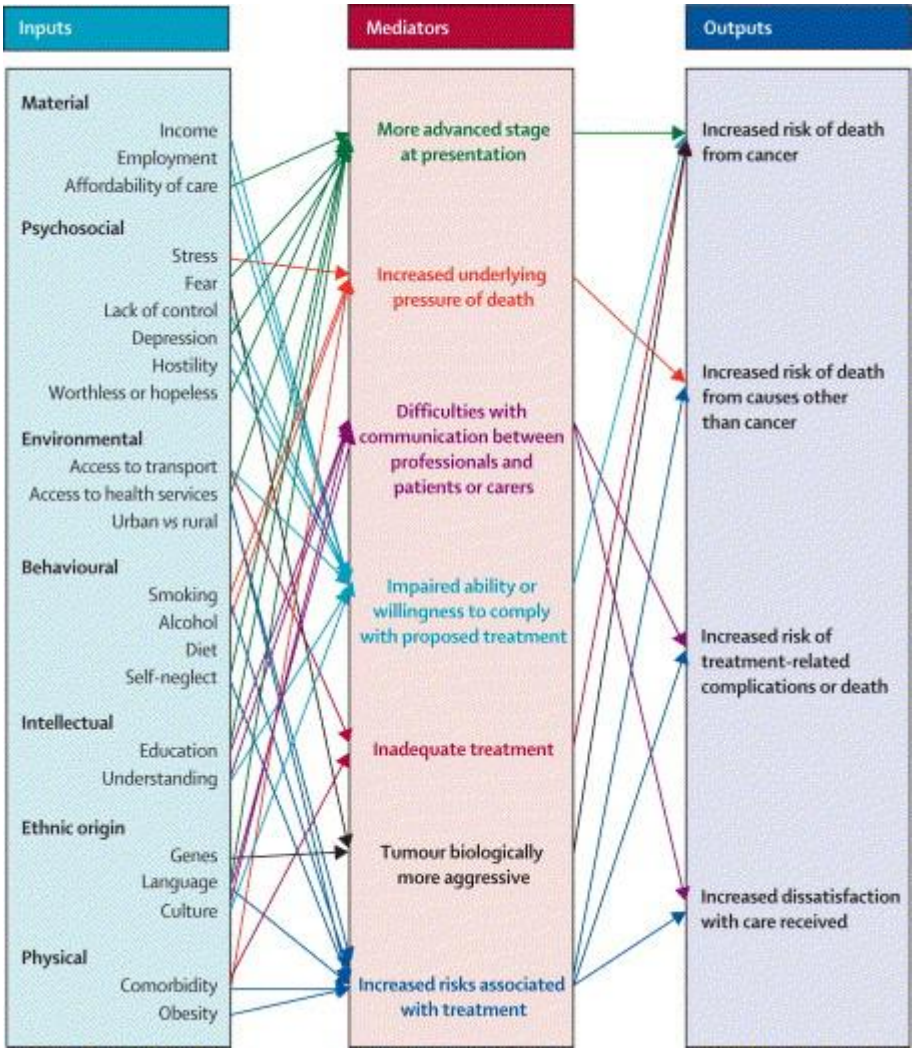
It is well known from population studies of life expectancy that people from poorer (deprived) backgrounds die younger and this group tends to have a higher proportion of disease compared to their affluent counterparts. A social gradient of health status and social class was first observed in the census of 1851 and this situation has not changed. As pointed out by Deaton,

"mortality and morbidity rates are inversely related to many correlates of SES such as income, wealth, education, or social class."(106) As a concept, SES in itself has not been consistently defined nor has it been consistently measured. (107) SES, has been defined as a function of income, education and occupation, although it is not the cause of cancer or poor outcomes, but it is a marker for underlying physical and social factors that cause disease, disease recurrence and reduced survival. (108) SES can be identified as an individual's relative position on the social hierarchy.

It is important to study the impact of low SES (deprivation) in cancer as there is a plethora of evidence demonstrating the effect of SES on cancer incidence and mortality. A working definition for deprivation describes it as, "a demonstrable disadvantage to others and consists of material disadvantage, diet, income, housing etc. and social disadvantage such as, relationships in family life, work and the community".(109) In Scotland, Conway *et al* (110) were able to ascertain the widening socioeconomic inequalities in oral cancer incidence over a 30 year period. Similar findings were noted by other research teams for laryngeal, oropharyngeal and oral cavity cancers. It is expected that if inequalities in HNC incidence exist, there would be corresponding disparities in HNC survival based on socioeconomic factors.

There are various types of cancer that have a common contributing cause at the individual level such as tobacco smoking which is a known antecedent for cancers of the lung, breast and head and neck, but there may also be common socioeconomic causes at the population level i.e. due to social and cultural norms that influence behaviour. This complex mosaic of risk and predisposition to cancer is adequately depicted in the figure below (Figure 6) which demonstrates how difficult it is to decipher how patient characteristics such as socioeconomic deprivation can influence the incidence and outcome of cancer.

Figure 6 How socio-demographic factors lead to poor outcomes in cancer



Adapted from Munro (111)

Socioeconomic factors are closely linked to the main risk factors of cancer as poor people are more likely to participate in risky lifestyle behaviours e.g. sedentary lifestyle, poor diet, have obesity and excessive alcohol intake. Deprived groups have been found to be less likely to attend for screening meaning they are unlikely to have early identification of a cancer which has consequences on survival. (112) As previously described, HNC is a disease mostly associated with increasing age. Evidence abounds on how deprivation and increasing age are most strongly and consistently associated with premature death.

It is well established that health follows a social gradient, as health improves with increasing socioeconomic position, (113) but in spite of the relationship between poor survival and socioeconomic deprivation, this particular problem has been difficult to address. Numerous attempts to assess the effect of SES on cancer survival have been conducted however researchers have been unable to conclude how low SES had a detrimental effect on survival due to a lack of consistent measurement of SES. (114-116) It is important to combat this SES-related unequal morbidity and mortality burden in order to make realistic gains on cancer survival in Scotland in comparison with England.

A complete understanding of what contribution deprivation makes to poor survival data is necessary in establishing what is causing these inequalities in cancer survival. It is widely accepted that low SES patients generally have poor health status and experience higher incidence and mortality compared to people from other SES groups. Evidence is available that demonstrates how socioeconomic factors contribute to prognosis, as research in the 1980s concluded that poorer survival in deprived groups were indicative of the lack of awareness and understanding of the dangers of cancer. (117)

Socioeconomic factors are especially important to study as they have essential contributory effects to cancer incidence and survival. Most cancers are known to be caused by exposure to avoidable carcinogenic agents such as tobacco, alcohol and infection and e.g. evidence shows that smoking related cancers are highest in deprived groups. Krieger gave the definition that, "social inequalities… in health refer to health disparities, within and between countries, that are judged to be unfair, unjust, avoidable, and unnecessary and that systematically burden populations rendered vulnerable by underlying social structures and political, economic, and legal institutions."(118)

The Black and Acheson Reports illustrated how poverty is linked to ill health which explains how cancer patients share this vulnerability, as research has focused on survival disparities and the

practical means to tackle this issue as reduction of health inequalities is a key priority. (119, 120) For example, the introduction of the Scottish bowel cancer screening program aimed to reduce premature cancer mortality by 20%, but this is not enough, other prognostic variables such as SES and its effect should be considered. A major concern for health professional studying inequalities in health is that although the rates of relative survival are improving across the board, socioeconomic inequalities are increasing. Lower survival rates have been described in deprived groups and this gap had been widening since 1986 especially in women.(121)

It was established that low SES has an equivalent risk to well established aetiological behaviours such as tobacco use in the development of oral cancer.(122) The role of tobacco and alcohol in the development of oral cancer is well established but increased use of tobacco and alcohol in individuals with low SES as a coping mechanism for dealing with poverty further implicates the role of deprivation in the aetiology of the disease. However it remains unclear whether it is the deprivation or increased exposure to known carcinogens that increases the risk. (123) There is a definite difference in incidence of cancer by SES for all cancers except breast and prostate which show an inverse relationship.

1.4.2. SES measurement

SES has been measured using a variety of indices. Indices of deprivation identify areas of multiple deprivations at the small area level. Deprivation measures have been used to assess and monitor inequalities in health which is useful in developing more targeted policies and more informed fund allocation. This is essential in order to understand the drivers behind geographical variations in illness and how this illness determines patient outcomes. Deprivation or low SES is usually measured at the individual level using information such as education, occupation and income. Unfortunately not all this information is usually available hence measurement at the geographical level was introduced to counter this shortcoming.

Initially the Carstairs and Morris Index (124) was used as an area based (postcode sector level) measure of deprivation following development using the 1981 census data to measure SES on four variables namely, overcrowding, male unemployment, low social class and ownership of a car. Categories are 1 for most affluent to 7 for the most deprived. The Scottish Index of Multiple Deprivation (SIMD) is similar to the aforementioned index as it looks at health inequalities across Scotland using small area concentrations (data zones) of multiple deprivations consistently. (125) The SIMD 2009 version is an improvement of earlier versions of SIMD 2004 and SIMD 2006. It now provides a relative measure of area concentrations of deprivation combining 38 indicators across seven domains which are; income health, employment, education, housing, crime and geographical access data.

The improvements made in methods of aggregating SES, means that analysis of the relationship between SES and HNC survival will elicit more meaningful data. There has been an association found between low income and poor levels of education with shorter cancer survival times compared to those with higher incomes and better educational attainment.(126) Carstairs and Morris found that variations in morbidity and mortality from specific diseases were linked to area level of deprivation in Scotland. (127) Comparison with England did not elicit any similarities so it is unlikely that poverty alone was contributing to this variation that coined the term "the Scottish effect". From this, it appears as though the excess burden of poor survival can be explained to some extent by deprivation. Therefore deprivation is an important prognostic factor in patients with cancer. From this it is clear that Scotland has a problem of widening health inequalities especially as a significant population live in deprived communities.

1.5.1. Comorbidity and SES in HNC

Cancer has socioeconomic implications, with higher incidence in and poor prognosis in the deprived groups. It is possible that deprived people are more prone to less favourable outcomes

due to poor dietary habits and lifestyle practices such as smoking and drinking to excess. From this, it is apparent that socioeconomic factors are just as important as behavioural risk factors, as stated by Broder, "poverty is a carcinogen".(128) Woods *et al* found that risk of cancer related death was increased up to 1.5 times in deprived versus affluent groups.(129) It is essential to study socioeconomic differences in cancer survival data as this may explain the differences in the diagnosis and treatment of HNC, as an IARC review showed an association between survival outcomes and SES. (130) Intertwined in this is that cancer outcome was determined by cancer stage at diagnosis with deprived groups more likely to have poorer outcomes compared to affluent comparisons. Numerous research studies have found the link between SES or deprivation and poorer health outcomes, (119, 131) and it is fair to say this is the same when addressing cancer survival outcomes.

This issue is of particular importance in Scotland as described by the then Chief Medical Officer that, "with deprivation comes a higher burden of disease, poorer uptake of services and worse outcomes of care".(132) Unemployment is a key element of the socioeconomic determinants of health as unemployed males have been shown to have an excess cancer mortality of 25% compared to employed men. Excess cancer deaths were found to be 70% higher in men and 41% higher in women when comparing most deprived backgrounds to least deprived. (133)

It has been established that people from deprived backgrounds have an unequal burden of mortality. (19, 134) Incidence of HNC is also very high in this group but it is unclear whether this difference is due to the differential distribution of cancer related risk factors. (135) There is an uneven distribution of high-risk behaviours and poor lifestyle choices amongst deprived groups, which may explain the variation in HNC incidence. This clustering of disease spells an almost inevitable outcome of poor survival rates in patients of deprived backgrounds. It is not clear why despite all the medical advances, there continue to be inequalities in health determinable by

deprivation status. As described by Tudor-Hart, "the availability of good medical care tends to vary inversely with the need for it in the population served. (136)

The literature demonstrates that survival decreases with age. This may be due to older people having a higher frequency of comorbidity resulting in late presentation of late stage cancers which generally causes less favourable outcomes. SES has also been implicated in determining poor survival. It is possible that social class differences are caused by cancer stage at presentation for diagnosis. (137) There have been notable gains in survival statistics in affluent groups which may explain why deprived people have less favourable outcomes. Several studies have demonstrated the link between poor survival and the presence of comorbidities specifically for HNC. (138-140) It remains unclear why survival disparities exist between socioeconomic groups but Woods *et al* (129) have implicated differences in comorbidity status, access to treatment, and treatment choices, stage of disease at diagnosis and tumour biology. Although the effect of comorbidity and SES has been addressed individually, no studies have been identified that consider the combined effect of comorbidity and deprivation on HNC survival.

As stated by Valderas *et al*, "a relatively new concept that is emerging is how influences such a patient's SES, behavioural and cultural influences can contribute to the physiological complexity of a cancer diagnosis occurring in the presence of a comorbid disease". (82) It is worthy to note that the relationship between deprivation and health status (comorbidity) is not fully understood despite the common place nature of both deprivation and concurrent chronic disease.(141) This illustrates the complex and intertwined nature of morbidity within the backdrop of other non-health related characteristics which was highlighted earlier. (111)

Richards reported that there had been a notable change in survival rates in the UK between deprived and affluent groups and although improvements are being observed in both groups, in order to explain the survival disparities, it appears now that, "clinicians attribute the deprivation gap to comorbidity". (142) Based on this assertion, it makes sense to review what contribution

socioeconomic deprivation makes to the survival outcomes of HNC patients. Additionally, the cancer community can no longer continue to ignore the obvious prognostic importance of these factors. The continued focus on the description of the tumour while ignoring suitable descriptions of the cancer patient weakens the scientific accuracy of the cancer staging system and ultimately the humanistic care of patients.(143)

1.5.2 Why study comorbidity and deprivation?

Comorbidity may produce or exacerbate inequities in health outcomes between population groups with evidence internationally for the role of comorbidity in social class inequalities. (144, 145) Deprived patients have higher prevalence of comorbidity, and are more likely to have multiple, complex comorbidity than their more affluent counterparts. (139, 146-152) HNC and the comorbidities normally found in HNC patients share many common risk factors. These include age, smoking, and alcohol abuse which are all risk factors for a range of common non-cancer conditions including diabetes, hypertension, respiratory, cardiovascular and peripheral vascular disease and liver disease, and are also risk factors for HNC. (153, 154) 13 studies (11, 89, 143, 148, 155-163) all examined the prognostic importance of comorbidity. These studies were able to demonstrate that comorbidity is a predictor of survival in HNC. Diagnosis of HNC occurs in the 5th to 7th decade of life which means that a patient will usually have comorbidity. The presence of comorbidity was found to affect treatment selection, which in turn, may have an impact on survival. (11, 16, 155, 164)

Although chronological age was not identified as an indicator of frailty, it does have an influence on treatment choices. (11) Apart from having comorbid disease and being elderly, an HNC patient has other vulnerabilities. The issue of chronological age compared to biological age has to be taken into consideration alongside other patient factors such as deprivation. A patterning of social inequality in a Danish cohort found an inverse relationship between HNC incidence and

social position (SES) with evidence of lower survival rates in the socioeconomically disadvantaged, i.e. the deprived (165) with confirmation of these findings in a later study. (11) There have been various theories developed to explain the reason for these disparities but despite adjusting for factors such as tumour biology, tumour stage at diagnosis, amongst others the survival differences between socioeconomic groups have prevailed. (129) There are different ways of assessing social contributors to health across the developmental spectrum, with risky behaviours such as smoking and drinking being major causes of ill health in adulthood compared to long-term exposure (e.g. to viral infections) in childhood. (166) Of note, the main antecedents of HNC are smoking and drinking to excess, which also follow a social patterning as the most deprived are more likely to drink and smoke more heavily than their affluent counterparts.(167-169) In this instance it is unclear whether deprivation is the risk factor (128) or whether the social norms of high-risk lifestyle behaviours of deprived groups are to blame.

Concurrent medical conditions (comorbidities) accumulate and complicate an HNC patient's health status even as SES can compound this disadvantage leading to poor survival. As Boeje *et al* (11) advocated further scrutiny of how patient related factors impact prognosis; this thesis will explore this complexity presented by patients with head and neck diagnosis who have co-occurring disease and the interplay of SES on survival. Comorbidity is common among people with HNC, due to the aetiology and epidemiology of this form of cancer. Comorbidity has an impact on HNC outcomes, and its impact is in part, modifiable. The same cannot be said for SES which as a social construct is beyond the control of the patient. The interest lies in identifying the role of comorbid conditions specifically in relation to treatment and survival for cancer.

The gap in the literature that is the focus of this project is that despite numerous research studies on how either comorbidity or SES affect survival in patients diagnosed with HNC, before now there have been no previous attempts to investigate whether both factors were interrelated in determining survival. The survival disadvantage that is predetermined in the presence of

deprivation and severe comorbidity in patients face in comparison to their counterparts has never been investigated. It was unknown if this disproportionate mortality experience could be due to both factors as most studies only used comorbidity as a predictor as they adjusted for SES as it was considered a confounder. It was decided to establish whether deprivation did have a confounding effect in analyses of comorbidity or whether deprivation and comorbidity had measurable effects as prognostic factors. In addition it was essential to assess whether the prognostic association changed when the factors were assessed independently or in combination. The decision was made to focus on comorbidities in isolation from or ahead of other patient factors (age, gender, smoking, alcohol, behaviours), tumour factors (site and stage), and treatment factors on HNC survival because the systematic review research question had to specific and concise in order to formulate a sound literature search that obtained the most relevant research papers. Research has shown that the TNM classification is no longer enough to predict prognosis hence the need to focus on the patient related factors such as comorbidity and SES amongst others. In addition, the effect modification properties of the variables such age, smoking and alcohol status was taken into consideration which is why these factors were included in the retrospective cohort analysis. It appears that there is a case-mix difference in HNC where important factors such as HNC sub-type, treatment effects, comorbidity and deprivation all have a significant impact on survival.

1.6. Aims and objectives

Aim: The project will investigate the roles and interrelationships of comorbidity and deprivation on HNC survival. The project will investigate (a) what effect SES and comorbidity have on survival in HNC patients, b) whether there are differences in the presentation of HNC based on the levels of comorbidity and deprivation; a key secondary question is whether patients with lower SES present with more advanced cancer compared to their counterparts. In addition, a broad set of

secondary questions will ascertain whether there were differences in the prevalence of the HNC subtypes by SES in the Fife and Tayside communities.

1.7. Chapter summary

This chapter explained what HNC is and also what comorbidity and SES are as factors that influence survival. Measurement methods of these two concepts were discussed and a rationale for why these two factors needed to be evaluated within the context of HNC survival. The aims and objectives were set out for this project. The next chapter will report on a systematic review of the literature as a follow up to the introduction given in Chapter 1. The systematic review will appraises the evidence on the impact that comorbidity and deprivation have on survival in patients with HNC.

Chapter 2

2.1. Systematic review

2.1.1. Chapter outline

This chapter will describe in detail how a systematic review of the literature investigating the effect of SES (deprivation) and comorbidity on survival was performed. A summary of the findings from the narrative synthesis and meta-analysis of included studies will be given along. The overall survival estimates will be given in terms of the risk of death that both comorbidity and SES place either as independent prognostic factors or in combination. The chapter will conclude with how the systematic review of the literature recommended and influenced the development of future work.

2.2. Systematic review background

HNC is the collective term for cancers that occur in specific parts of the head and neck region. They usually (90% approximately) begin in the squamous cells that line the moist, mucosal surfaces inside the head and neck (for example, inside the mouth, the nose, and the throat). These squamous cell cancers are often referred to as squamous cell carcinomas of the head and neck. HNCs can also begin in the salivary glands, but as this form of HNC is relatively rare within the UK. Although these cancers are different, their treatments are similar so it makes sense to group them especially as the multidisciplinary teams (MDTs) which handle treatment follow set guidelines on treatment of HNC e.g. Scottish Intercollegiate Guidelines Network (SIGN) which are used in Scotland. Another issue that makes the grouping of HNCs easier is that they all share largely similar risk factors i.e. alcohol and smoking are all confirmed as aetiological factors with a multiplicative and additive risk for HNC based on degree of exposure. Although use of the collective term for HNCs is common there are inherent shortfalls due to peculiarities of the

specific HNC subtypes. This is especially the case for cancers that occur at the back of the tongue and in the tonsils (cancers of the oropharynx) have become more common over the last 2 decades. These cancers are mainly attributable to infection with a type of virus called human papilloma virus in particular type 16 (HPV 16). The main cause of HPV infection is that the virus spreads to the mouth and throat through oral sex, with a corresponding increase of risk of infection based the number of oral sex partners, although this trend is more evident in younger patients who tend to be from affluent backgrounds. (27, 50) Another type of HNC is that of the outer lip which is caused by exposure to sunlight particularly those who work outdoors (1in 3). So for the purposes of the systematic review, the collective term of HNC was used with a plan to assess the prognostic impact of each individual cancer in the cohort analysis.

In the UK, as in most other countries, HNC is more common in males than females, although this trend appears to be changing in Scotland due to the time lag of excessive smoking in females (note the similarity to lung cancer statistics). (170) Older adults are more prone to additional chronic diseases and these can exacerbate or be exacerbated by cancer which is especially pertinent here as cancer, like other chronic diseases, is largely related to advancing chronological age hence the relatively more common HNC diagnoses in Scotland as the fifth highest incident cancer as Scotland has an ageing population. (171) The typical HNC patient is usually male, older, and likely to have multiple comorbidities. (172, 173) It is believed that being older accords a greater likelihood of cancer diagnosis as increasing age equates to an increasing vulnerability to age related health problems such as heart disease, hypertension, diabetes, arthritis and COPD i.e. comorbidities which compound the prognosis of HNC. (146, 174)

Concurrently, within the UK there is a distinct north-south gradient of cancer morbidity with rates higher in the north (Scotland) than Wales and England to the south. (175) Although this phenomenon has been observed for a number of decades, the exact cause has not been

identified. Some researchers have pointed towards the influence of socioeconomic deprivation but this may not be the sole determinant for this inequality. (128, 176)

The relationship between age, chronic disease and cancer can be compounded further by disparities such as SES. Health inequalities remain an important public health issue in cancer care within the UK. In reviewing the issue of inequalities in health, the contribution of poverty to ill health had been identified in the 1940s but the medical profession had no control over this social aspect of disease manifestation. (177) Notably this relationship has prevailed with worse outcomes of disease occurring more commonly in the worse off (deprived) within society. However with the continued advances in personalised medicine it is important to understand how socioeconomic status affects survival outcomes in order to adjust for this when devising treatment approaches within HNC oncology.

Socioeconomic, environmental, cultural, biological/genetic and behavioural factors all have an impact on survival. (98) The ability to assess prognostic factors in patients is an important aspect of cancer treatment and control .(178) Although there have been advances in the care and treatment of HNC, there remains evidence of survival disparities between and within populations, as seen in Table 3.

Table 3 Scottish HNC incidence and mortality by SES

	INCIDENCE				MORTALITY			
SIMD 2009 deprivation quintile	**Number of registrations**	**EASR**	**- Lower 95% CI**	**- Upper 95% CI**	**Number of death registrations**	**EASR**	**- Lower 95% CI**	**- Upper 95% CI**
5=Least deprived	632	9.5	8.8	10.3	190	2.7	2.3	3.1
4	814	12.1	11.2	12.9	240	3.3	2.9	3.8
3	1,009	15.2	14.2	16.1	336	4.7	4.2	5.2
2	1,335	21.4	20.2	22.6	469	7.1	6.4	7.7
1=Most deprived	1,571	28.8	27.4	30.3	618	10.8	9.9	11.7
Test for trend (Poisson regression)	<0.0001				<0.0001			
Sources: Scottish Cancer Registry, ISD (incidence); National Records of Scotland (NRS) (mortality and populations)								
Notes:								
1. Rates are calculated using the populations in 2009.								
2. Cancer registration is a dynamic process: the data presented here may differ from other published data relating to the same time period.								
3. Confidence intervals for age-standardised rates (EASR) have been calculated using a formula which works only								
when numbers are sufficiently large. They are therefore set to 'not applicable' in the event of there being 50 cases or less.								
4. For analyses using SIMD 2009: ISD have changed their labelling and now label the categories as 1=most deprived to 5=least deprived.								
Our policy of population-weighting the quintiles remain unchanged, so the datazones contained within each quintile will differ slightly to those presented in Scottish Government releases.								
EASR: age-standardised incidence rate per 100,000 person-years at risk (European standard population)								

Source: ISD Scotland (26)

This makes the case for a shift in focus from the use of time proven prognostic factors such as the TNM classification alone. Research conducted has demonstrated the prognostic importance of social health determinants. (166, 179-182) The stage at diagnosis is an important prognostic factor as the earlier the diagnosis, the better the outlook. There is evidence of a social gradient in HNC as deprivation is associated with late stage HNC, which could be due to delayed presentation due to poor health awareness levels and high exposure to risk factors such as smoking and drinking. (108, 116, 130, 135, 183-186) Although these characteristics are important, it is also imperative to account for the general health status of the patient, including the degree to which comorbidity influences the intervention of choice, the risk of complications and the outcomes of treatment. (187)

Comorbidity is the simultaneous existence of several diseases, and can be prognostic or therapeutic. Therapeutic comorbidity pertains to the clinical course of cancer which can be altered by drug interaction and/or polypharmacy. This is the case in laryngeal cancer where COPD as the co-existing illness results in treatments that have to be administered differently because these patients tend to receive radiotherapy rather than chemotherapy to reduce the risk of toxicity of medications.(188)

Prognostic comorbidity is how comorbid disease/diseases affect survival. This is due to the how co-existing illnesses can potentially alter both the efficacy of therapies and the course of the primary disease, thereby contributing to premature death. In other words, it can pre-exist HNC (particularly in older people) or it can develop during the clinical course of the index disease.(1, 143, 147, 150) Comorbidity occurs more frequently in the elderly who are more prone to developing cancer, therefore posing considerable challenge to treatment selection. Additionally, survival outcomes are wholly dependent on how well both the cancer and the comorbid disease(s) are managed. (189) The field of prognostication of disease now focuses on the important role of comorbidity and not only on the conventional TNM (tumour-node-metastasis)

classification as comorbidity has been found to have a negative effect on outcomes, whether tumour or treatment related. Previously this relationship was put down to confounding, but after controlling for common confounders such as age, gender and race, tumour stage and site, the relationship has remained significant, demonstrating that comorbidity is an important prognostic attribute of cancer. (178, 189) Physiologic burden of chronic disease and cancer equate to poor outcomes as it is believed that the clinical course of HNC can be altered by comorbid disease as this form of cancer affects older patients who are more likely to have coexisting disease. (90, 156, 190-193)

Overall it is important to assess how these patient factors; comorbidity and socioeconomic deprivation affect outcomes in HNC patients because:

- Deprivation may be described as both a risk and prognostic factor for HNC,
- Comorbidity has been posited as a confounder and prognostic factor in HNC

Therefore these two patient factors should be considered in HNC survival.

2.2.1. Literature scoping

Prior to the main review, a scoping search of the literature was done with the aim of determining the existence of a systematic review on this subject. This scoping exercise also helped to clarify what literature was available pertaining to comorbidity and deprivation in HNC outcomes. A preliminary search of databases such as the Cochrane Library, Intute, MEDLINE, CINAHL, Centre for Reviews and Disseminations (York CRD) and Health Technology Assessments was made to identify whether a systematic review of this topic had been previously conducted. There was one study reported as a systematic review of socioeconomic status and cancer (194); however after mapping of the evidence and critical appraisal of the paper, it was found to be methodologically flawed . This review did not search all possible sources for relevant primary studies while the included studies were not quality assessed hence there was no way of reproducing any aspects

of the research. (195-197) There was no evidence of similar research being previously conducted within the HNC field, however a similar study reviewing the survival of patients from deprived backgrounds with comorbid disease had been carried out in colorectal cancer. (145)

2.2.2. Systematic review rationale

Despite the plethora of evidence relating to factors determining survival in HNC, there is an overwhelming lack of evidence of the systematic appraisal of the evidence demonstrating how comorbidity and SES together impact survival outcomes. HNC although the 6th most common incident cancer in the world, (20) has survival estimates of approximately 60% (97) which have only experienced marginal improvement in the last three decades. HNC is a potentially life threatening diagnosis and as such it is imperative to evaluate the influence of any factors that may reduce the risk of death in affected patients. As mentioned previously there is very little research around the role of comorbidity and SES in determining the survival of HNC patients. Focusing on these prognostic factors is imperative to as there have been very little increase in survival figures. The evidence base to determine the effect of both factors on outcomes is either incomplete or unavailable.

HNCs are often associated with older age, low SES and high levels of comorbidity. In spite of this knowledge, the relationship between SES and comorbidity and how they combine to impact on survival is unclear. The systematic review investigating the extent to which comorbidity and SES are associated with survival in patients with HNC was conducted in order to help clarify this issue. A systematic review was chosen as it is the best research method to elicit and summarise all existing primary research on the issue under study.

A few studies have been conducted that have focused on either comorbidity or SES but interestingly all these studies have largely been heterogeneous in their findings. A single paper

(145) that attempted to address the systematic review aim was not on HNC and failed to identify the effect of either factor independently or in combination.

A systematic review of this topic was felt to be appropriate due to the considerable lack of research in this area. It is quite clear that if any review studies do exist, these are as yet unpublished or have not been evaluated rigorously or been validated as providing robust evidence of prognostic effect. Therefore, this review hopes to draw on an unexplored area in HNC survival.

A systematic review is justifiable here as it can help to propose a future research agenda as the way forward in HNC prognostication as the current route appears unclear. Recent epidemiological shifts such as the increase in HPV-positive HNCs have shown improved survival but patients with HPV-negative HNCs remain at a marked disadvantage with little chance for improved outcomes as the mechanism explaining the prognostic impact of comorbidity and SES remains unclear. It is hoped that this review will successfully integrate a meta-analytic approach alongside the narrative synthesis in order to develop an evidence base to better inform health policy and practice around HNC oncology.

HNCs are often associated with older age, low SES and high levels of comorbidity. In spite of this knowledge, the relationship between SES and comorbidity and how they combine to impact on survival is unclear; hence we conducted a systematic review investigating the extent to which comorbidity and SES are associated with survival in patients with HNC.

The main aim of this review is to consider the extent to which comorbidity and SES affect survival in HNC patients. Of particular importance is the comorbidity that pre-exists HNC and that directly occurring as a consequence of HNC. In terms of SES this refers specifically to the socioeconomic level of those diagnosed with any form of HNC. SES can take the form of individual, household or neighbourhood (small area statistics) where available. There is a rationale for a systematic review in this instance as there is a substantive question about the individual roles and whether an

interrelationship between comorbidity and deprivation exists. Several primary studies do exist, all pointing to the detrimental effects of both factors; however, an analysis of how both affect survival has not been evaluated prior to this review. This review will endeavour to pull together all the available research in this area of HNC and make meaningful conclusions about comorbidity and deprivation and their relative contribution to survival.

2.3. Systematic review aim

The aim of this review was

- To assess how the relationship and interrelationships of comorbidity and deprivation affected survival in patients diagnosed with HNC.

2.3. Hypothesis

The working hypothesis of the systematic review is that comorbidity and deprivation individually or in combination increase the risk of premature death in patients with HNC. The review seeks to understand the influence each factor's contribution to survival for HNC patients. We believe that these two factors work together to reduce chances of survival.

2.4. Methods overview

The application of the Centre for Reviews and Dissemination systematic review guidance aided the research approach to this systematic review; reducing bias, providing an audit trail and making certain that the methods used were explicit and systematic, with some elements such as the search strategy reproducible. The reporting of this review follows the instructions defined in the Meta-analysis and Systematic Reviews of Observational Studies in Epidemiology (MOOSE) guidelines (198) which are shown in Appendix 1.

The review encompassed 4 stages:

1. A reproducible literature search to locate relevant studies
2. The application of the inclusion/exclusion criteria to select studies to include in the review.
3. Methodological quality assessment and data extraction
4. Synthesis of systematic review findings

2.4.1. Inclusion criteria

To reduce publication bias, (199) this review considered all published sources without restrictions to geographical setting. The following criteria were used to assess studies for inclusion:

- Location- unrestricted
- Language- English or where translation was possible
- Time frame- no restrictions
- Population- patients diagnosed with any form of HNC
- Outcome of interest- survival
- Study type- Primary research assessing contribution of comorbidity and/or deprivation

2.4.2. Exclusion criteria

This review excluded the following:

- Survival studies of skin cancers of the head and neck,
- Studies of survival outcomes in other cancers found in the head and neck area but not covered by the definition of HNC given previously,
- Studies involving expert opinions, editorials, commentaries and secondary research papers,

- Studies written in any languages where translation was unavailable.
- Studies focusing on racial disparities
- Studies of incidence rates of head and neck cancers (HNC) were excluded because as they did not report survival outcomes for those with the disease.
- Studies that focussed on cancer in general but without specific reference to HNC and those that focused on HNC definition grouped to include oesophageal cancer or thyroid cancer were also excluded.
- Case control studies were also excluded from this review as they do not have high generalisability although their internal validity is quite high. They tend to be more useful in determining diagnosis and also because they use 'outcome selective sampling'. (200-202) Also the other limitations of case control studies include the risk that selection of cases and controls may be biased such that groups differ systematically in unknown ways. (203, 204) One might argue that the trade off between cohort and case control studies may be limited as the accuracy of cohort studies is dependent on the accurate collection of medical records. Nevertheless, cohort studies were included as they provide the strongest evidence for observational studies of prognosis. (205)

2.4.3. Application of the inclusion/exclusion criteria

Based on the stepwise approach to systematic reviews, the inclusion and exclusion criteria were applied to all the studies retrieved from the systematic literature search. Data arising from the review were used to make evidence-based recommendations regarding the prognostic importance of comorbidity and socioeconomic deprivation in the survival of patients diagnosed with HNC.

2.4.4. Outcome of interest

This review was conceptualised to investigate survival in patients with head and neck cancer with survival classified as a single outcome measure, namely death. Death from all causes is an objective measure of outcome and it was used here to consider the following outcomes:

- Disease free survival
- Overall survival
- Disease (tumour) specific survival
- Death (mortality)

The outcome measures used, as reported in the studies, should also meet the criteria of reliability, validity and feasibility.

2.4.5. Protocol deviations

The protocol was followed as much as possible in terms of the research question that needed to be answered. At the beginning of the project, the area of research was meant to be in four cancers; breast, head and neck, prostate and colorectal. While trying to devise the literature search, the principal investigator realised that focusing on HNC would give a clear and concise assessment of the relative contributions of comorbidity and deprivation in determining patient survival. Preliminary searches for each cancer had given the principal investigator a preview into the size of the workload and as colorectal cancer had previously been researched with same objective, it would be difficult to justify redoing the retrospective data analysis after the systematic review. As very little was known the combined effect of deprivation and comorbidity in head and neck cancer and as it became clear early on during the literature search that there was a paucity of studies focusing on both prognostic factors and their influence on survival in head and neck cancer, this focus on head and neck cancer was justified. Following discussion

with the principal investigator's supervisors, it was agreed that HNC would be the focus the ensuing work. Unfortunately due to unforeseen circumstances the protocol was not registered.

2.4.6. Search outline

The aim of this research was to obtain all the relevant observational studies that focused on the effect of deprivation and/or comorbidity on survival. In order to devise a systematic and reproducible literature search, a formative search of the literature was done in MEDLINE followed by analysis of the text words contained in the title and abstract as well as index terms of an article pertinent to this review (206) From this pilot search, search terms were developed for the systematic literature searching. The search terms were identified using a variety of sources, including an examination of previous systematic reviews of a similar topic, brainstorming and an examination of database thesauruses and this resulted in a final list of free-text search terms.

A detailed text and MeSH heading search strategy was carried out after consultation with a medical librarian and a colleague who specializes in systematic reviews (see Appendix 3 for details of the search strategies). The search strategy involved a systematic and reproducible search from various peer reviewed data sources to identify published literature based on the inclusion and exclusion criteria. To increase the sensitivity and specificity of the records obtained, the researcher consulted the university librarian and also used other research experts for advice on the search strategy. As a result the search strategy used relied heavily on free text wording to improve the specificity of the search. Survival was chosen as the outcome of interest, rather than recurrence; as the date of death is more likely to be measured accurately and the results for survival are easier to interpret than those for recurrence.

From this initial search, a systematic search strategy was constructed in MEDLINE from the list of key words and index terms to retrieve articles to consider for the inclusion in the systematic review. A final extensive search using all identified keywords and index terms was then used to

devise adapted search strategies for different bibliographic databases and sources adding in relevant thesaurus terms specific to each database. The search terms used were designed to identify studies that indexed or pertained to (i) Head and neck cancer (HNC), (ii) survival analysis/prognosis and (iii) socioeconomic status (deprivation) and/or comorbidity status, or their synonyms. The search strategy included key terms for cancer (neoplasms OR cancer OR tumour), AND comorbidity (additional disease OR coexisting disease OR additional morbidity), AND survival or prognosis (survival analysis OR survival rate OR proportional hazards model OR survival OR prognosis).

All search terms were 'exploded' in conjunction with using a keyword search. It was anticipated that most of the identified studies would be cohort studies; however, all observational study designs were eligible. The databases included were

- EMBASE (1980–Feb. 2012), updated to January 2015
- MEDLINE (1966–Feb. 2012), updated to January 2015
- LILACS (1975–Feb. 2012),
- CINAHL (2012), updated to January 2015
- SciELO (up to Feb 2012) and
- ISI Web of Science (1980–Feb. 2012), updated to January 2015

All search strategies (original and updated) are presented in the Appendix. The search included an iterative process to refine the search strategy through testing of several search terms and incorporation of new search terms as new relevant citations were identified. An attempt to use optimum search strategies of studies of prognosis devised by Wilczynsk and Haynes for use in both EMBASE and MEDLINE proved to be poor at obtaining relevant studies. (207, 208)

To ensure the search strategy for this review was systematic and sensitive enough to pick up all the relevant studies, a further citation search was done from the reference list and bibliographies of all identified reports and articles that were retrieved from the searches detailed previously. The reference lists of all papers and relevant reviews identified were assessed for any additional

papers meeting the inclusion criteria. The electronic sources listed above were searched for all relevant studies regardless of the studies' publication status, (in press, published, unpublished and in progress). An initial updated search was conducted again between January and February 2012 and redone in January 2015 in order to obtain any other publications that may have been missed in the initial search. A systematic search of the literature was done for English, Spanish and Portuguese-language studies that reported survival of patients with a diagnosis of HNC. Language was extended beyond the English language as translation facilities were accessible for Spanish, Portuguese, Polish and German languages. In the end only Spanish and Portuguese papers were included as they met the inclusion criteria.

A further cited reference search was conducted in Web of Science on the relevant papers and used the "related articles feature" in SciVerse Science Direct. After reviewing the "related articles" and "cited reference" search results and finding only 22 potentially eligible articles shown in Appendix 4, this part of the search process was concluded. The review process required many methodological decisions not fully anticipated in the initial protocol. These included issues regarding inclusion criteria and study eligibility based on methodological quality.

2.4.7. Filtering and article selection

All references identified were loaded onto Endnote. This reference management software was used to track and maintain an audit trail of all studies as they passed through the review process. The first reviewer (EM) conducted an initial filtering of all references in order to exclude obvious irrelevant references and duplicates located in the database searches. The excluded references were checked by a thesis supervisor (CM) in the group to ensure no relevant references had been excluded at this point.

The titles and abstracts for these citations were then independently examined by the author (EM) and her supervisor (CM) with a third reviewer (MW) consulted where there was

disagreement, which additionally helped to ensure consensus was reached. The full text paper was retrieved if the abstract mentioned all of the following

(i) patients with HNC;

(ii) overall survival, HNC-specific survival or recurrence;

(iii) comorbidity or SES.

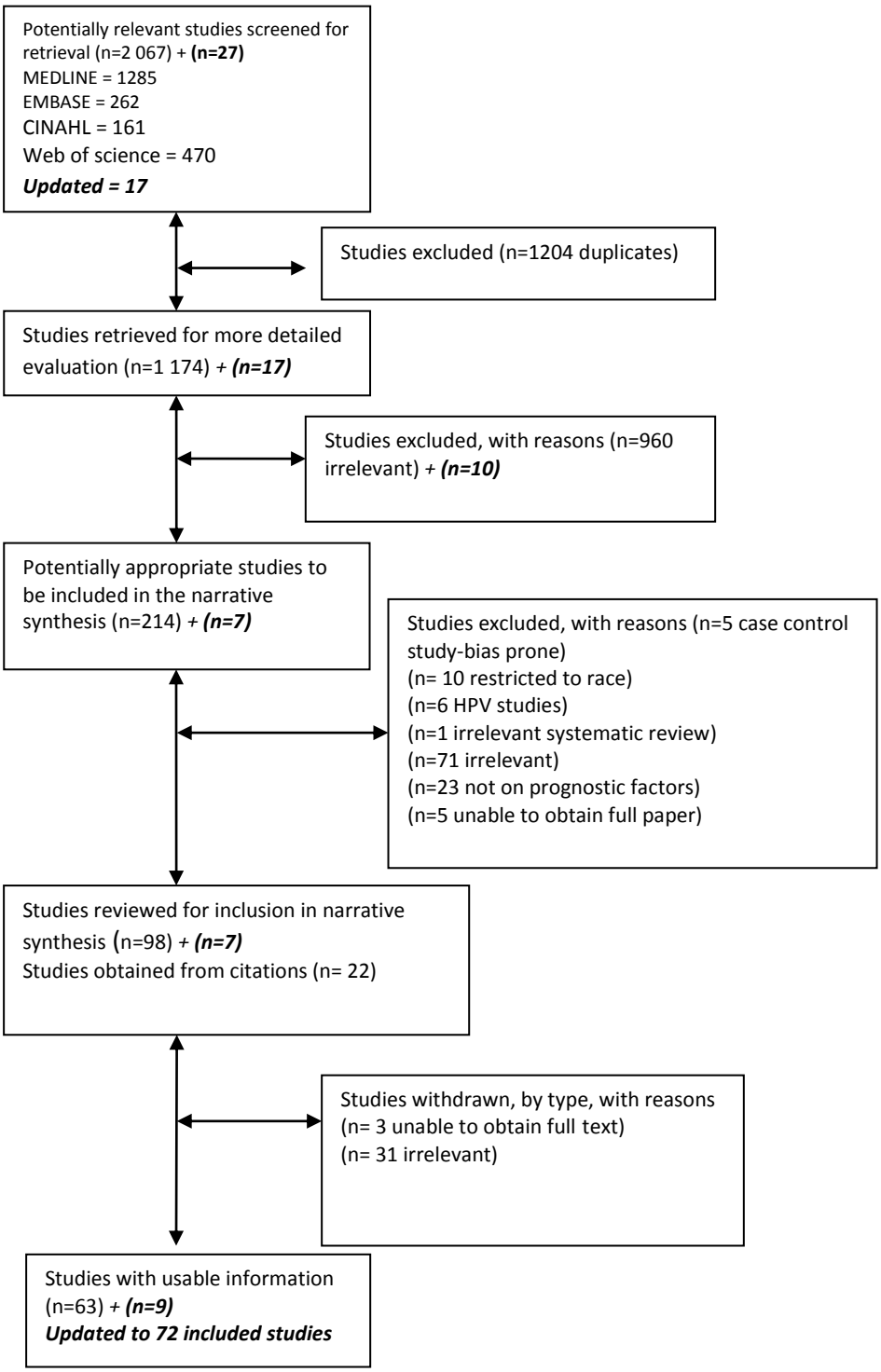
The initial search identified 2067 potentially eligible studies but on further review these were reduced to 1174 using the following methods:

- Title and abstract review
- Full text of paper review

An updated search was conducted in January 2015 and 4 papers (209-212) focusing on SES were identified and 3 papers (213-215) on comorbidity.

The full outline of how the search was initially conducted in order to obtain the final sample of papers is depicted in the flow chart; the new papers from the systematic review updated literature search are in italics.

Figure 7 Flowchart of included studies



Adapted from the PRISMA flow diagram (216)

Footnote explaining PRISMA

Definition of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. The flow diagram depicts the flow of information through the different phases of a systematic review. It maps out the number of records identified, included and excluded, and the reasons for exclusions

2.5.1. Development of the methodological quality assessment tool

There is increasing volume of literature that focuses on prognosis in head and neck cancer. Despite these advances in this field, there has not been a corresponding plethora of literature on methods to assess the quality of prognosis studies. Although guidelines exist that explain reporting of observational studies (STROBE, REMARK, MOOSE), as yet there does not appear to be any guidance on how to conduct a systematic review of prognosis studies. Systematic reviews of prognostic studies are very complex to undertake as the methods for this have not been standardised unlike those for therapeutics or diagnostic reviews, as stated by Altman (202) and confirmed during the conduct of this review.

There are no established criteria for assessing the quality of survival studies, therefore the author initially set out to use the McMaster University Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies. Quite quickly the author realised that this tool was not fit for purpose as it was more geared towards intervention studies. Therefore a search of the literature was conducted to investigate whether a pre-existing quality assessment tool for observational studies could be located. Originally a prognostic quality assessment tool developed by the University of Montreal (217) was considered for use but this was found to be more suitable for a professional measuring prognostic likelihood for a specific patient.

A search of the literature on critical appraisal pointed to two tools that were potentially eligible for use either based on their own merit or with minor adjustments. (218) Both these tools proved inadequate to provide complete and concise critical appraisal and quality assessment of the included studies. (219, 220) Due to the difficulties faced in obtaining a validated quality assessment tool on evaluation studies, following discussions between the review team members, the decision was made to devise a tool for use in this review. An initial draft was based on work conducted by different researchers, and adapted into a tool. (202, 217, 221, 222) A pilot quality assessment of 20 papers was conducted by the author (EM) and the third reviewer (MW). The

purpose of this was to assess whether the quality assessment process was free from bias and fairly amenable to a systematic approach, while assessing the validity of each article, and determining its importance within the context of this review. This pilot quality assessment found a lot of inconsistencies as all the studies reviewed rated as strong although both researchers acknowledged that using basic critical appraisal skills, some of these studies had methodological flaws, hence a 'strong' quality rating was inaccurate.

The methodological quality assessment tool was revised using more rigorous research evidence. (202, 203, 223) Also to minimize the possibility of different interpretations of each appraisal question, a dictionary of the meaning of each question was devised to make this tool useful and adaptable for future projects.

Two reviewers, the author (EM) and the second supervisor (EW) independently assessed each study then discussed their ratings together. Any disagreements were discussed and resolved by consensus agreement and final discussion with the thesis supervisor (CM) as the third reviewer.

2.5.2. Assessment of study eligibility

Reviewers (EM, CM, and MW) were not blinded to the included studies identified for full evaluation in the screening process. Two reviewers, (EM and CM) independently assessed all studies identified for inclusion and resolved disagreements by discussion. For papers deemed eligible, the author and third reviewer (MW) with access to the full paper reviewed the eligibility decision. For the systematic review update EM had sole input to conducting the study eligibility exercise.

Key of systematic review team

1st reviewer – Author (EM)
2nd reviewer – Thesis supervisor (CM)
3rd reviewer – Collaborator (MW)

2.5.3. Data abstraction

The principal researcher alongside three reviewers independently assessed the quality of included studies and abstracted data from all eligible studies; they resolved disagreements through discussion. Information relevant to the methodological quality of the studies included the study design, the populations selected (criteria inclusion in the primary study and the degree to which the studied population was representative of the wider universe of patients with the diagnosis), measurement of outcome (that is, the extent to which the outcome measures were defined similarly, and monitored similarly), loss to follow-up, and the extent of risk adjustment for confounders that might affect prognosis. Other data obtained during data abstraction included the country in which the study was conducted, the period of observation, the number of participants, and the main outcomes. Studies were classified as being of high, moderate or low quality according to the criteria used in the quality assessment tool developed by the lead investigator using data from other studies.

2.5.4. Data extraction strategy

Data from the final sample of the studies meeting the inclusion criteria was extracted and summarized in data abstraction forms, see Appendix. For the quantitative studies the data collected for extraction included the following:

- Details of the publication (study author, country, year)
- Number of study participants
- Tumour site
- Prognostic factor and measurement method (of comorbidity/SES)
- Data analysis method
- Survival analysis reported/endpoints considered: (median, overall, 3 or 5-year survival.)

- Adjustment for confounding
- Methodological quality rating

2.6. Review findings

Due to the diversity of the sources of evidence used in this review, it was felt that attempting a meta-analysis of both comorbidity and SES studies would be problematic. This was mainly due to the heterogeneity of the study measures used as the comorbidity was measured using different indices e.g. ACE-27, CCI, WUHNCI, Kaplan Feinstein, etc. Similarly, SES was quantified differently using individual/household income, education and using aggregate measures such Index of Multiple Deprivation etc. The following reasons also posed uncertainties in the use of meta-analysis to summarise review findings: -

- Inadequate reporting of methods used- some authors did not explain in adequate detail
- Different measurement techniques were used- comorbidity and SES measured differently
- Variation in methods of analysis- some used Cox regression, life table method and Gray's test etc.

A formal meta-analysis of all studies was not attempted due to variations in study populations, and SES markers used. However, a meta-analysis was done for the comorbidity studies grouped by comorbidity index which resulted in separate analyses for ACE-27 and Charlson Comorbidity Index (CCI) studies. All the other studies' findings were presented in narrative format.

Based on these findings, both the meta-analytic and narrative synthesis were the most appropriate methods to report the results of this review.

This review grouped included studies into two separate entities namely:

i. Comorbidity studies using both meta-analysis and narrative synthesis where appropriate
ii. Socioeconomic studies – narrative synthesis only.

In essence two parallel reviews were conducted simultaneously in order to answer the research question. Following the concurrent synthesis of findings for both arms of the review, a final synthesis was devised to bring together the emergent themes in the results.

The aim was to integrate the findings of the two syntheses to investigate the prognostic impact of both SES and comorbidity in HNC survival.

2.6.1. Results from search strategies

The systematic search of the literature identified 124 potentially relevant studies that had information on HNC alongside estimates of survival. Of these nine studies were rejected as they focused solely on race.(224-233) One of these studies by Gourin *et al* (226) was restricted to treatment selection rather than survival hence it was excluded. Similarly a study was rejected as it focused on treatment choice in the elderly accounting for comorbidity. (234) Specifically a paper by Sethi *et al* did not meet the inclusion criteria as it reviewed compliance with treatment, (235), Six papers did not meet the inclusion criteria as they examined the influence of human papilloma virus positive (HPV+) status which is not a relevant prognostic factor based on the specified definition of this review. This is because HPV is not a comorbidity but rather a risk factor for oropharyngeal cancers.(60, 63, 69, 236-238) Five papers that were case control studies which were excluded due to risk of systematic bias and imprecise measurements in part due to selection and information bias as well as confounding.(239-243)

The paper by Menvielle *et al* (244) was rejected as the defined HNC used in this paper included oesophageal cancer which does not conform to the HNC definition used in this review. Moles *et al* (245) focused on the increased socioeconomic gradient in oral and pharyngeal cancer but did not elaborate on survival, therefore it was excluded from the systematic review. Several other studies in much the same way were rejected for not reporting survival estimates (246-249). Twenty-three papers did not focus on how comorbidity and/or socioeconomic status contributed

to prognosis hence these papers were excluded from the analysis. (164, 248, 250-270) (164, 248, 250-270)

The paper by Antunes *et al* (271) was rejected as it was a comparison of Brazil vs. Spain without any reference to how comorbidity and/or deprivation were linked to survival. Another paper was excluded as only the abstract was available and did not provide adequate information for detailed evaluation (272). Four papers were excluded due to failure to obtain full text.(273-276) Six papers did not focus specifically on HNC hence did not meet inclusion parameters. (277-282) A paper was also excluded from the analysis for focusing on comorbidity (myocardial infarction) occurring after HNC diagnosis.(283) Six papers did not focus on survival outcomes (prognosis) hence they were discarded from the analysis, (15, 253, 284-288) while a paper on delayed diagnosis was excluded as it did not focus on survival. (289)

The study by Alho *et al*, (156)was rejected as it reported on the same cohort as the more recent paper by Teppo et al (290) which was included. Similar inclusion was made of the paper by Grignon *et al* (291) while the later one (292) was discarded as it looked at first year trends of the earlier studies. One study was described as a survival study but on closer inspection it did not meet the inclusion as it was a survival trend analysis of England and Wales, rather than a cohort study. Two papers did not have sufficient data to allow complete evaluation.(293, 294) Quality of life is a function of survivorship rather than survival hence studies that looked at this were also ruled out.(122, 295, 296)

Second primary cancers are not a comorbidity hence papers focusing on this did not fulfil the inclusion criteria. (297, 298) Papers that centred on comparison of comorbidity indices without reference to survival were also rejected.(148, 163, 299-301) Two studies did not meet the inclusion criteria as they were reviews rather than primary studies, (302, 303) while another was also excluded as it was a systematic review of the literature, (304) and yet another was a commentary. (305) Casasola *et al's* (306) epidemiological paper and Piccirillo's editorial were

deemed irrelevant because they did not give data on survival.(139) Two papers were rejected as they did not evaluate survival despite the influence of comorbidity from depression and Fanconi's anaemia respectively. (307, 308) Another paper by an anonymous research team was rejected due to issues of relevance to the research question.(94) From the cited reference only two papers (309, 310) and the remaining 20 studies (69, 163, 225, 237, 240, 257, 258, 260, 261, 280, 281, 311-318) were excluded from the analysis.

From the systematic review update the following articles were rejected following full text review, (231, 302, 319-324)

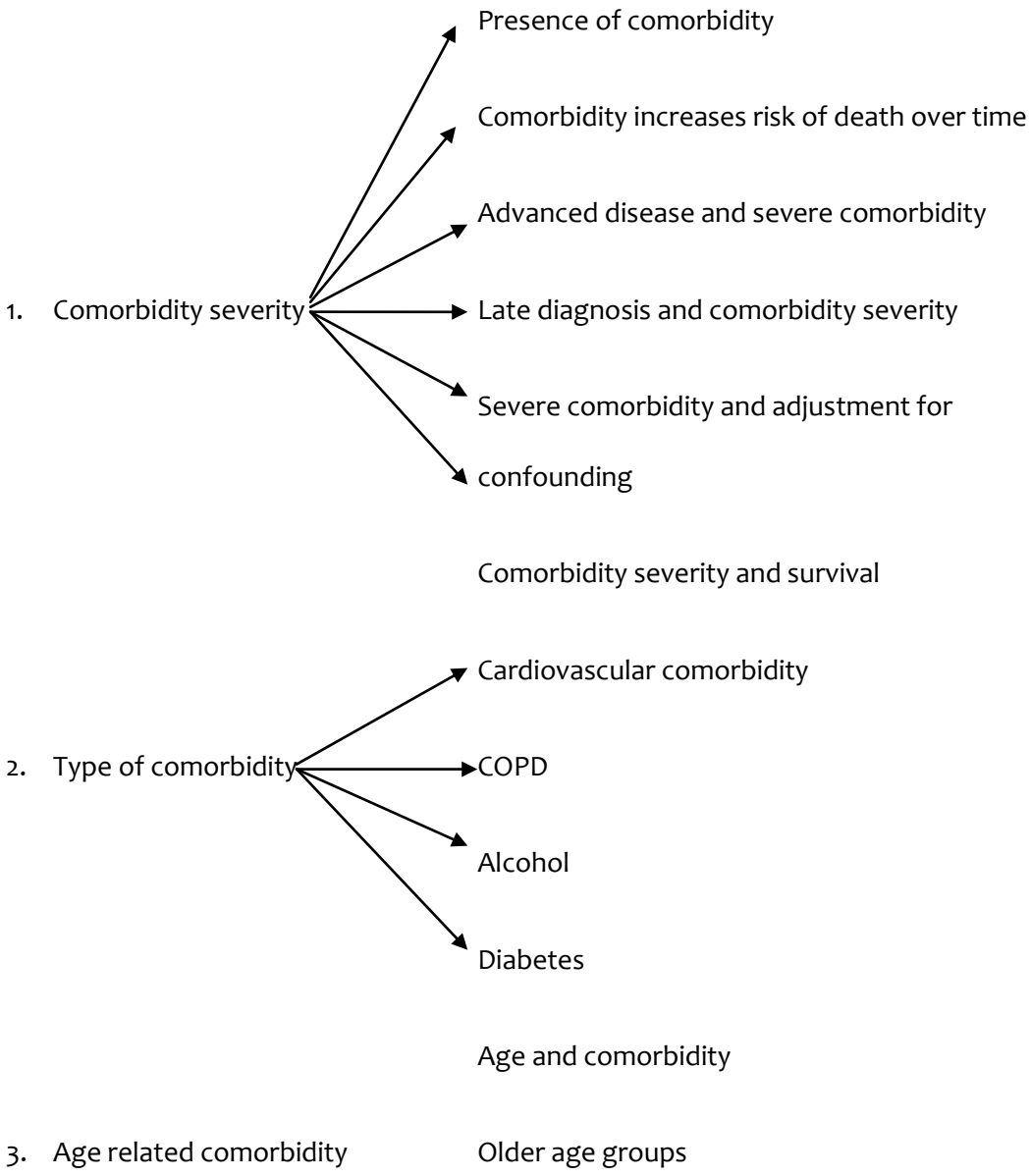
2.7.1. Narrative synthesis methods

Narrative synthesis methods were employed to organise findings to provide an initial descriptions of patterns emerging across the included studies. (325) This was done using the following sequence with the comorbidity data presented as an example of the narrative synthesis process:

- Textual descriptions: a short 'story' with key messages, significant information that acts as a 'viewing platform'.
    - Age and disease stage
    - Severe comorbidity and disease stage
    - Presence of comorbidity
    - Diabetes as a comorbidity
    - Late diagnosis and severe comorbidity
    - Comorbidity increasing risk of death over time
    - Severe comorbidity and adjustment for confounding
    - Alcohol as a comorbidity
    - Advanced disease and severe comorbidity

- Age and comorbidity
- Older age groups
- Comorbidity severity
- Late diagnosis and severe comorbidity
- COPD in laryngeal cancer
- Comorbidity severity and survival

- Ordering/grouping: finding shared features and clustering studies along those lines



- Common rubric: Using a common framework to allocate material from multiple studies.

1. Severity of comorbidity increases risk of death
2. Types of comorbidity and effect on mortality
3. Age and comorbidity have an effect on risk of death

2.7.2. The chosen approach

The studies included in this systematic review all underwent quality assessment and critical appraisal with ratings of strong, moderate and weak given on the basis of methodological quality. Various measures were used in the SES studies ranging from validated indices of deprivation, education, health insurance status, occupation and income. Due to the variety of evidence of survival predicted by socioeconomic status all the study findings will be reported regardless of their overall quality rating.

2.7.3. Meta-analytic methods

In head and neck cancer (HNC) a cure may not be possible, but it is hoped that taking account of a patient's general health status may increase the duration of survival.

The rationale for not incorporating the studies that quoted their cohort's survival using odds ratios (OR) and relative risks (RR) is that they measure only the number of events and take no account of when they occur are and therefore these methods are not entirely appropriate for analysing time-to-event outcomes. (326) Time-to-event data are most appropriately analysed using hazard ratios (HRs), which take into account of the number of events including when each event occurred they also take account of censored patients (the time until last follow-up for each patient who has not experienced an event). The studies that did not use the necessary statistics to allow estimation of the HRs will be discussed later in a narrative summary of results.

The statistical methods used here are based on methods described by Tierney *et al* (326) when HR and their confidence intervals are given. The following equation is used:

$$V *= [\ln \quad (upper\ 95\%\ CI) - \ln \quad (lower\ 95\%\ CI) \div 2 \times 1.96].$$

The methods described by Sutton and colleagues (327) to approximate the hazard ratio as the effect size was used alongside the inverse variance method to conduct the meta-analysis.

The meta-analysis was conducted using Microsoft Excel 2007 to calculate standard errors as well upper and lower confidence limits of these. This data were inputted in to survival analysis package (328) within the R statistical software using the meta-analysis program to conduct the statistical methods.

Effect size estimates were grouped into sets according to comorbidity severity. Each study could contribute only one effect size per point in time. If a study had multiple comorbidity effect sizes, these were included in separate analyses dependent on comorbidity classification to represent the study effect on a particular comorbidity level. The variability of effect sizes was assessed using the *Q statistic* to test for heterogeneity. The *Q statistic* has an approximate chi-square distribution with *k-1* degrees of freedom in which k represents the number of effect size estimates.

A significant *Q* rejects the null hypothesis of homogeneity and supports the search for possible moderating variables. The fixed effect model is thereby used to examine systematic influence of moderating variables and overall effect size estimates. The use of the random effects model was selected over the fixed effects model as it was assumed that sources of variance associated with distribution of effect sizes were likely to be randomly distributed. As defined by Hedges, (329) the study sample is presumed to be literally a sample from a hypothetical population or collection of studies. Another benefit is that generalisations from findings of random effects model can be applied to a large variety of situations not reflecting similar considerations to those of the studies used in the meta-analysis.

2.7.4. Findings

63 studies were eligible for inclusion in the review as detailed in the study flow chart. This increased to 72 studies once the systematic review was updated. The studies were from diverse geographic regions with the majority of papers coming from the USA. They focused on a variety of HNC subtypes and were mostly retrospective in design; see the data abstraction table in the Appendix.

2.7.5. Results of the meta-analysis

Adult Comorbidity Evaluation-27

Mild decompensation vs. no comorbidity

Seven studies were identified to investigate the likelihood of death due to mild comorbidity, which is defined as ACE-27 group 1 or mild decompensation. Of these, four studies crossed the line of no effect however the other three demonstrate a statistically significant increase in risk of death. From the results depicted in the forest plot, it shows that mild comorbidity has an effect on survival. The risk of death does not cross the line of no effect, hence showing the prognostic impact of comorbidity. The Q statistic of 15.2 with p value: 0.018 shows there is some heterogeneity between the studies, while the random effects model shows a clear increased risk of death with a hazard ratio of approximately 0.3.

Table 4 Risk of death in Mild decompensation vs. no comorbidity (ACE-27 1)

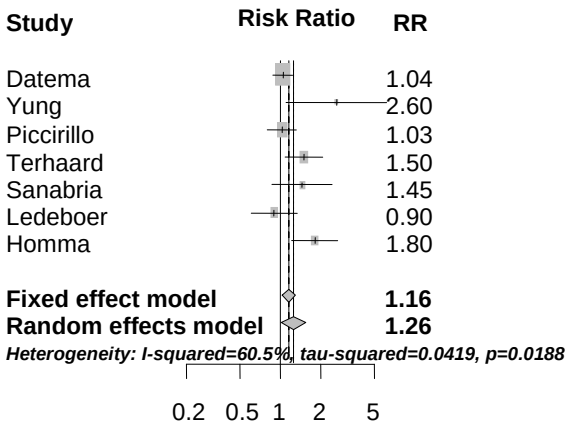
Study Name	Effect estimate	95% CI	%W(fixed)	%W(random)
Datema (330)	0.042	[0.1285; 0.2125]	44.08	22.57
Yung (150)	0.956	[0.0917; 1.8203]	1.72	4.72
Piccirillo (147)	0. 030	[0.2209; 0.2809]	20.36	19.15
Terhaard (331)	0.405	[0.0816; 0.7284]	12.25	16.15
Sanabria (155)	0.372	[0.1396; 0.8836]	4.90	10.15
Ledeboer (332)	0.105	[0.4911; 0.2811]	8.60	13.83
Homma (160)	0.588	[0.1901; 0.9859]	8.10	13.43

		95%CI	z-score	p value
Fixed effect model	0.1474	[0.0342; 0.2607]	2.5528	0.0107
Random effects model	0.2280	[0.0209; 0.4351]	2.1577	0.031

Quantifying heterogeneity: tau^2 = 0.0419; H = 1.59 [1.05; 2.41]; I^2 = 60.5% [9.5%; 82.8%]

Test of heterogeneity: Q: 15.2 d.f.: 6 p.value: 0.0187

Figure 8 Mild decompensation vs. no comorbidity (ACE-27 1)



Moderate decompensation vs. no comorbidity (ACE 27 2)

This forest plot (Figure 9) demonstrates an exponential increase in risk of death for patients with moderate comorbidity. Only two studies show no effect but the pooled hazard of death has increased to approximately 0.5. Heterogeneity is evident with *Q* of 29.99, df: 7 and p value of <0.0001. Both the fixed and random effects models show similar point estimates but the influence of smaller studies such as Yung *et al*, (150) Tanvetyanon *et al* (333) and Soares *et al* (334) have pulled the effect size to the right. The wider confidence interval shows wider variability in the results of the pooled studies within the random effects model. This model shows that moderate comorbidity reduces survival.

Table 5 Moderate decompensation vs. no comorbidity (ACE 27 2)

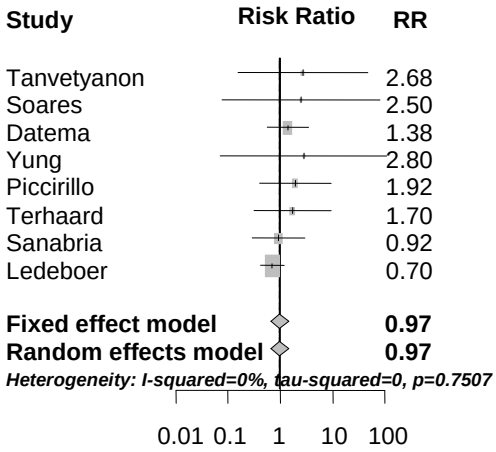
Study name	Effect estimate	95% CI	%W (fixed)	%W (random)
Datema (330)	0.321	[0.1407; 0.5013]	43.84	17.70
Yung (150)	1.030	[0.1617; 1.8983]	1.89	7.09
Piccirillo (147)	0.652	[0.4031; 0.9009]	23.00	16.68
Terhaard (331)	0.531	[0.1645; 0.8975]	10.61	14.61
Sanabria (155)	0.083	[0.6004; 0.4344]	5.32	11.89
Ledeboer (332)	0.357	[0.7510; 0.0370]	9.18	14.11
Tanvetyanon (333)	0.986	[0.4098; 1.5622]	4.29	10.91
Soares (334)	0.916	[0.0399; 1.7921]	1.86	7.01

		95%-CI	z	p.value
Fixed effect model	0.3887	[0.2693; 0.5080]	6.3805	< 0.0001
Random effects model	0.4277	[0.1358; 0.7197]	2.8714	0.0041

Quantifying heterogeneity: tau^2 = 0.1169; H = 2.07 [1.47; 2.92]; I^2 = 76.7% [53.5%; 88.3%]

Test of heterogeneity: Q: 29.99 d.f.: 7 p.value: < 0.0001

Figure 9 Moderate decompensation vs. no comorbidity (ACE-27 2)



Severe decompensation vs. No comorbidity (ACE-27 3)

This figure shows that severe comorbidity accords a corresponding increase in risk of death compared to nil comorbidity. There is no evidence of heterogeneity between all the studies in the meta-analysis as Q: 13.29 d.f.: 7 p.value: 0.0652. There is also no difference between the random and fixed effects models. The risk of death which had experienced a steady increase by comorbidity severity for both mild and moderate comorbidity levels continued to increase with risk of death pooled estimate of approximately 0.8, demonstrating a significant reduction in survival for patients with severe comorbidity compared to those without comorbidity.

Table 6 Severe decompensation vs. no comorbidity (ACE-27 3)

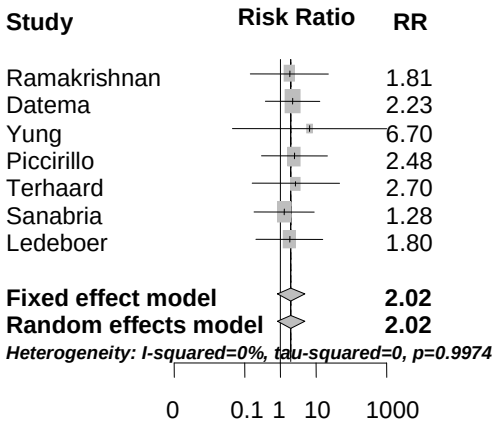
Study Name	Effect estimate	95%-CI	%W(fixed)	%W(random)
Datema (330)	0.802	[0.5492; 1.0548]	39.69	22.39
Yung (150)	1.902	[0.9906; 2.8134]	3.05	5.87
Piccirillo (147)	0.908	[0.5709; 1.2451]	22.33	18.93
Terhaard (331)	0.993	[0.4227; 1.5633]	7.80	11.42
Sanabria (155)	0.247	[0.3998; 0.8938]	6.07	9.73
Ledeboer (332)	0.588	[0.0706; 1.1054]	9.48	12.81
Grignon (291)	0.215	[0.4318; 0.8618]	6.07	9.73
Ramakrishnan (162)	0.593	[0.0851; 1.2711]	5.52	9.12

		95%-CI	z	p.value
Fixed effect model	0.7731	[0.6138; 0.9324]	9.5123	< 0.0001
Random effects model	0.7509	0.5039; 0.9978]	5.9596	< 0.0001

Quantifying heterogeneity: tau^2 = 0.0543; H = 1.38 [1; 2.07]; I^2 = 47.3% [0%; 76.6%]

Test of heterogeneity: Q: 13.29 d.f.: 7 p.value: 0.0652

Figure 10 Severe decompensation vs. no comorbidity (ACE-27 3)



Charlson Comorbidity Index

Mild/moderate comorbidity vs. no comorbidity (CCI 1)

Only one study (290) did not show a statistically significant relationship with risk of death from comorbidity measured by the Charlson Comorbidity Index. The remaining 3 studies clearly indicate decreased survival prospects for patients with mild or moderate comorbidity. The *Q* statistic of 6.29, with df: 3 and p.value of 0.0982 is not significant hence the random shows there may be some variation due to study sample size.

Table 7 Mild/Moderate comorbidity vs. No comorbidity (CCI 1)

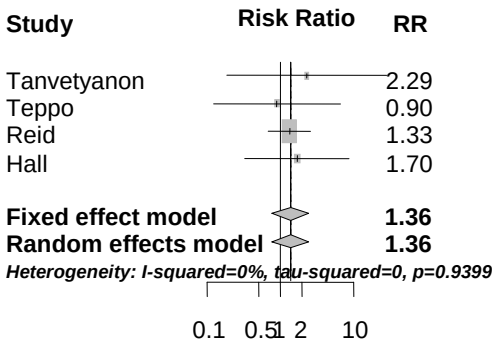
Study Name	Effect estimate	95%-CI	%W(fixed)	%W(random)
Tanvetyanon (333)	0.829	[0.2939; 1.3641]	2.98	16.69
Teppo (290)	0.105	[0.9576; 0.7476]	1.17	8.19
Reid (335)	0.285	[0.1870; 0.3830]	88.91	47.99
Hall (294)	0.531	[0.1802; 0.8818]	6.94	27.13

		95%-CI	z	p.value
Fixed effect model	0.3137	[0.2213; 0.4061]	6.6541	< 0.0001
Random effects model	0.4106	[0.1445; 0.6767]	3.0240	0.0025

Quantifying heterogeneity: tau^2 = 0.0359; H = 1.45 [1; 2.52]; I^2 = 52.3% [0%; 84.2%]

Test of heterogeneity: Q: 6.29 d.f.: 3 p.value: 0.0982

Figure 11 Mild/moderate vs. no comorbidity (CCI 1)



Severe comorbidity vs. no comorbidity (CCI ≥2)

A notable increase in risk of death is observable for severe comorbidity than no comorbidity. This hazard has increased to approximately 0.7. One of the larger studies (336) shows no effect but all the other studies show a statistically significant relationship between comorbidity level and likelihood of death. The test of heterogeneity shows a: 71.79 d.f.: 8 p.value: < 0.0001, showing that there is random variation between the studies included in this meta-analysis. These studies suggest potential decreases in survival due to comorbidity severity.

Table 8 Severe comorbidity vs. No comorbidity (CCI 2)

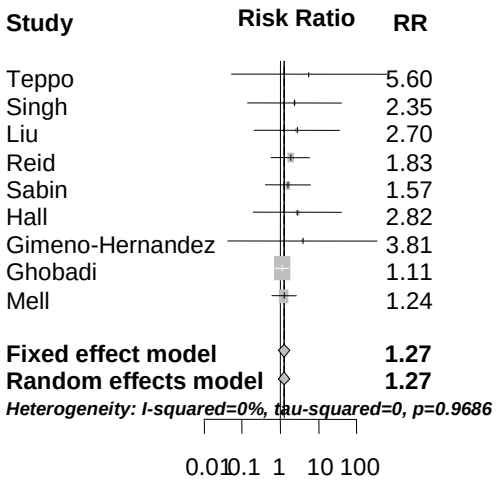
Study name	Effect estimate	95%-CI	%W(fixed)	%W(random)
Teppo (290)	1.723	[0.8391; 2.6069]	0.58	5.56
Singh (163)	0.854	[0.2092; 1.4988]	1.08	8.04
Liu (337)	0.993	[0.5402; 1.4458]	2.20	10.82
Reid(335)	0.604	[0.492; 0.7157]	36.10	15.81
Sabin (276)	0.451	[0.1668; 0.7352]	5.58	13.59
Hall (294)	1.037	[0.5725; 1.5015]	2.09	10.63
Gimeno-Hernandez (338)	1.338	[0.3071; 2.3689]	0.42	4.50
Ghobadi (336)	0.104	[0.0077; 0.2157]	36.10	15.81
Mell (339)	0.215	[0.0464; 0.3836]	15.86	15.23

	95%-CI	z	p.value
Fixed effect model	0.3832 [0.3160; 0.4503]	11.1883	< 0.0001
Random effects model	0.6484 [0.3915; 0.9052]	4.9473	< 0.0001

Quantifying heterogeneity: tau^2 = 0.1054; H = 3 [2.3; 3.91]; I^2 = 88.9% [81.1%; 93.4%]

Test of heterogeneity: Q: 71.79 d.f.: 8 p.value: < 0.0001

Figure 12 Severe comorbidity vs. No comorbidity (CCI 2)



2.8.3. Narrative synthesis

Comorbidity and SES

The literature searches detailed in Appendix A2 yielded 72 studies for inclusion in the review. Of these, three studies used both comorbidity and SES, 25 studies were on SES and the remaining 44 were on comorbidity. The reporting format for this section of the review will commence with the studies that focused on both factors under review followed by comorbidity and SES studies.

Only three studies from the USA and The Netherlands were found to report on both comorbidity and SES. (335, 340, 341) The findings of the first of these studies by Gourin *et al*, (340) were deemed incomplete as no data was provided on survival based solely on the prognostic factors of interest, i.e. comorbidity and SES. The researchers focused on comparing patient survival by stratifying both prognostic factors by race. They were able to show the disparities in survival, notably that black patients had poorer prognosis at 29.3% compared to 54.7% ($p<0.0001$) for whites. Although there was no evidence for variation in comorbidity status by race, advanced comorbidity levels appeared to be indicative of poor survival for all patients with a disease specific survival (DSS) hazard ratio of 1.436 ($p=0.0005$), while overall survival had a hazard of 1.482 for ($p<0.0001$). (340)

Another study from the USA found that with each incremental level of comorbidity, the hazard of survival also decreased.(335) However, after accounting for other factors such as age, the prognostic impact of comorbidity was reduced. This team of researchers also investigated the effect of SES on outcomes measured by household wealth, but this did not demonstrate an association with survival.

The study by Allareddy *et al* (341) found evidence to demonstrate that comorbid disease was linked to reduced survival measured using in hospital mortality and this relationship remained significant even after controlling for confounders. Likewise patients who were on Medicaid or

were uninsured had worse survival when weighed against privately insured patients. The severity of comorbidity appeared to be associated with a corresponding risk of poor survival, with advanced comorbidity increasing risk by up to 2 times than that of a patient with none/mild comorbidity.

Comorbidity only

Heterogeneous measurement of comorbidity meant 44 studies were not included in a meta-analysis. Notably Gimeno-Hernadez *et al* (342) found that disease stage has a significant impact on survival. They found that having advanced comorbidity with stage 1 or stage 2 disease increased the hazard ratio to 4.68 compared to only 2.08 in patients with stage 3 or 4 disease without comorbidity. One study adjusted for age, disease stage and comorbidity with a resultant hazard of death attributable to comorbidity status of 3.91. (160) These findings were similar to those of other studies which found a similar consistent trend of a 2-fold increase in risk of death.

Evidently comorbidity has a higher prognostic impact in the initial stages of disease unlike in more advanced disease stages when risk of mortality is unchanged. (343) In tandem with these findings, survival advantage was noted to change dependent on the presence of one or more comorbidities compared to none at all. Overall survival was noted to reduce from 26.3% for patients without comorbidity to 11.8% in patients with three comorbidities. (343) Singh *et al* also found that when comparing patients with mild versus those with severe comorbidity, the median survival intervals were different at 13.7 months and 57.6 months respectively. (163)

The severity of comorbidity was associated with reduced survival in a number of studies. (343) (344) (148) (187) (159, 161, 291, 332, 345) (160, 346) (18) (347-349) A 2 fold risk of death was apparent in patients with severe comorbidity, with Paleri *et al* noting that patients without comorbidity had median survival of 58.6months with a mortality rate of 11.1%. (299) Comorbidity and advanced disease resulted in poor survival with median survival at 12.3 months for the high

comorbidity group compared to 38.7 months for patients classed as having mild comorbidity. (160) Leitner *et al* reviewed deaths at 6 months, 1 year and 5 years after diagnosis, and comorbidity was noted to affect survival within the first year with rates of death starting at 2% and increasing to 6% by the end of the 5 year period. (345) It was apparent that comorbidity severity had a direct effect on survival as each incremental level of comorbidity contributed a 25%-35% increase in mortality risk at five years. (159, 291)

A recurring theme was that high comorbidity levels had a demonstrable impact on survival. Sanabria *et al* (346) found that after controlling for confounding, the hazard of death increased by 72% for ACE-27 ≥2 comorbidity group which is illustrative of the independent predictive importance in HNC survival for patients with severe comorbidity. These results corresponded with the later empirical findings of Ledeboer *et al* who recorded an 80% increase in hazard in patients with severe comorbidity (ACE-27 score 3) compared to those without comorbidity. (332) Additionally Sanabria *et al* had in their earlier study, noted that comorbidity severity contributed to reduced survival , but an alternative view by Sabin *et al* (155) had classified age as a comorbid condition which had reduced the relative risk of death from 1.5 to 1.36 however there were no other studies to support these results.

Age appeared to have a more pronounced effect on survival in the presence of comorbidity. Mell *et al* (339) found that comorbidity had a prognostic effect in older patients which is indicative of the nature of competing mortality (comorbidity) which can contribute to increased number of deaths attributable to cancer i.e. the index disease. Ramakrishnan *et al* (162) also pointed out that age and comorbidity in combination did not have an effect on prognosis but comorbidity had an individual effect that contributed to a high hazard of death with a RR=1.81. All in all increased symptomatology i.e. comorbidity and cancer combined to reduce survival. (140)

The severity of comorbidity was noted to have a prognostic impact on survival as Datema *et al* (344) established marked differences in the impact of comorbidity severity on prognosis, e.g. two

year survival probability in comorbidity grade 1 versus nil comorbidity was 67% and 75% respectively. Overall comorbidity severity was found to translate to a 2-fold risk of death and comorbidity type such as substance misuse posed the highest prognostic importance with grade 3 hazard of death at RR=3.2 compared to 1.9 for grade 1. These figures were much higher than cardiovascular and respiratory comorbidity which had hazards of 1.8 and 1.7 respectively. Zhang *et al* (349) were able to demonstrate statistically significant incremental increases in risk of death with corresponding increase in comorbidity severity with HR of 3.6 ($p<0.001$) for CCI ≥3.

In the presence of a specified comorbidity, in this case COPD in laryngeal cancer, more premature morbidity as a result of this co-existing disease was noted in patients aged ≥65 years with a 2-fold risk of death compared to patients aged 35-64 years. (350) Cardiovascular comorbidity was noted to significantly decrease survival while patients with two or more comorbidities had an elevated risk of premature death. (351) Notably alcohol was denoted in the causal pathway of HNC and in patients with alcohol-related health problems and alcoholism as a comorbidity, risk of death was increased 2-fold. (310) Diabetes mellitus in nasopharyngeal cancer patients was found to account for a lower disease free survival rates accounting for a 30% decrease in survival for diabetics compared to non-diabetics. These survival differences were especially apparent two years post-HNC diagnosis with a marked decline in survival for the diabetic group. (352) Comparable increases in risk were demonstrated in a similar study on diabetic comorbidity, with risk of death increasing to 2.22 ($p=0.008$). (347)

Late presentation appeared to increase the likelihood of premature death alongside severe comorbid disease equated to poorer survival with the relative risk of death increasing 5-fold in patients with advanced comorbidity, 3-fold in professional diagnostic delay and almost four times in patients with advanced clinical disease staging. Piccirillo *et al* found a strong dose response relationship between comorbidity severity and survival. (148) Similar findings by Montero *et al*

found that this translated to a twofold increase in risk of death from the highest comorbidity level compared to the lowest. (187)

Comorbidity was a good prognostic indicator as patients with mild/moderate comorbidity measured using the ACE-27 index classed as grade ≤2 had survival rates of 64% survival versus 29% in grade 3 patients. (96) Comparable findings by Chen *et al* (161) found a higher risk of mortality was evident in patients with moderate/severe comorbidity compared to those with mild/none with 5 year survival rates at 21.8% and 46.3% respectively. The study by Yang *et al* (348) revealed that lower comorbidity levels were also linked to better survival as 5 year OS decreased from 77% for CCI 0 to 40% for CCI ≥6 ($p<0.001$).

The odds of death in patients with comorbid disease was found to be OR=2.1 indicating a doubling in the risk of death in comparison to patients without comorbidity. Ramroth *et al* (214) noted an incremental decrease in 5 year overall survival (OS) and disease free survival (DFS) within their cohort with figures ranging from 73.4% to 52.1% (OS) and from 85.4% to 74.5% (DFS) for patients without comorbidity compared to those with severe comorbidity.

Despite this overwhelming evidence pointing to the negative effect of comorbidity on survival, one study by Sadat *et al* (215) was unable to reach similar conclusions. They found no statistical difference in survival for the presence of comorbidity, HR of 0.13 ($p=0.48$), although this finding may be explained by the lack of an instrument to measure comorbidity. Comparable findings from Peters *et al* (213) were noted using the ACE-27 index but this relationship disappeared once risk status was categorised dependent on presence of comorbidity and its corresponding severity with odds ratios (OR) ranging from 0.323 for mild decompensation to 0.435 for severe comorbidity ($p<0.001$).

Socioeconomic status studies

A meta-analysis was not attempted due to the heterogeneity of SES measurement. These studies will be reported as groups so that those looking at similar SES domains can be compared. This was done as SES in this review encompasses a variety of domains namely, education, age, indices of deprivation, household income, neighbourhood income, small area statistics, occupation and health insurance. The Carstairs index was used in four studies (309, 353-355). Disparities between affluent and deprived patients were evident and nasopharyngeal and UADT cancers poor survival was increased in deprived patients (354, 355), i.e. living in a deprived area is equal to an to 25% increase of risk of death in UADT cancers and deprived equated to a 24% higher likelihood of death from any cause (355).

Age appeared to play a role with Paterson *et al* (353) noting no survival differences between deprived and affluent patients in the younger age group (0-39 years). However those aged 40-59 years had survival rates of 59.5% for affluent patients vs. 52.4% for the deprived. In the 60-79 year age group relative survival rate were of 51.1% and 42% for affluent and deprived respectively. These results for the 40-59 years and 60-79 years age groups were showed a statistically significant linear relationship with $p<0.001$ for both age groups. (353) The more advanced the age, the lower the survival at five years, with rates of 76% for <50 years, 67% for 50-59 years, 56% for 60-69 years and 35% ≥ 70years ($p=0.01$). (356) There were significant differences in survival using the standardised rate ratios (SRR) between the most deprived and the most affluent groups. A notable pattern of reduced survival from most affluent to most deprived group was shown in males for mouth cancer but this was not so clear for either females or for tongue cancer in both sexes. (167). A comparable and more pronounced trend was shown in mouth cancer in males with SRRs increasing from 61 to 152 ($p<0.005$) for most affluent and most deprived respectively between 1986 and 1991. (167) Younger patients aged 0-44 years from deprived backgrounds were found to have a reduced likelihood of survival with HR=2.12

compared to less affluent patients HR = 1.19. (357) This result was highly statistically significant p=0.002. There were less clear patterns of risk for those aged ≥ 45 years with more affluent patients having a risk of 1.85 compared to 1.98 for less affluent patients. (357)

Continuing with age, Chang *et al* (210) found that deprived patients aged <65 years had worse survival compared to their over 65 less deprived opposite numbers (p<0.001). Even after adjustment using multivariate analysis, this survival relationship remained significant with increased survival rates of between 0.5 and 0.7 for those aged >65 years. The odds of lower survival experiences increased to approximately 1.5 and 1.7 for those aged less than 65 from disadvantaged neighbourhoods after adjustment for treatment modalities and hospital choice. (210)

Affluence was found to raise survival by 43% in NPC patients (p<0.001). (354) This was similar to findings for UADT cancers which showed that deprivation resulted in a premature reduction in survival of 41% for larynx cancer, 31% for pharynx and 28% for mouth cancers which compared to affluent patients. (355) Five year overall survival (OS) figures showed differences between social strata with affluence having OS of 53.9% in contrast to 42.3% in the deprived for oral cavity cancer while figures for larynx cancer were 68.4% in the affluent and 59.1% in the deprived. (309)

Area level SES measures generally found that more advanced disease was more common in patients from deprived backgrounds, (108, 358) and an inverse relationship between SES and survival. (108, 123, 167, 357-360) Material deprivation in females was implicated as the cause for poor survival in mouth cancer patients. (167) HNC was found to occur more commonly in the poor. (167, 357-360) Only glottis cancer was found to occur more commonly in older well-off patients (108), while there was no difference in the proportion of patients with disease in the study by Warnakulasuriya *et al* (357). Robertson *et al* (358) found that despite the negative survival experiences across the socioeconomic strata much of this effect was diluted by the confounding effect of performance status. The hazard ratio in univariate analysis was 1.33 but

was reduced to 0.93 (p=0.04) after controlling for sex, stage, site, performance status, alcohol and tumour differentiation.

Level of income was associated with improved survival from 3-23%, (108) with the relative risk (RR) with each incremental level of income from 1.47 for ≤ 20 000 to 1.07 for incomes between > 40 000 and ≤ 50 000. (359) Relative survival in the most deprived quintile was 2.75 for death from glottic cancer although supraglottic cancers did not show an association between income and survival. (108) However one study (361) found that family income as a measure of SES was not related to survival (p=0.05). Low neighbourhood SES was found to be linked to low disease specific survival (DSS), in cancers of the oral cavity, oropharynx, hypopharynx/larynx and nasopharynx. (362)

Evidence of a linear gradient in survival between income groups was evident as Rachet *et al* (363) found a reduction in survival of 17% for deprived groups compared to less deprived groups. Using neighbourhood income, Chu *et al* (364) found poorer survival for those from lower income groups. Jovanovic-Andersen *et al* (365) found evidence of similar gradients in survival based on SES which was akin to the findings of Boyd *et al* (209) who noted that for glottic cancer, relative risk (RR) was higher for the low SES groups . Comparable findings were noted for patients among oropharyngeal cancer patients from highly deprived neighbourhoods relative to less deprived neighbourhoods with poorer overall survival with a hazard ratio of 1.59. (366)

Income quintiles based on median household income were noted to give reliable estimates of mortality risk as survival from HNC decreased by 7.4% and 13.7% for Ontario, Canada and the USA respectively between quintiles 1 and 5. (209) Survival was also noted to decrease by income quintile in the same study. Lee *et al* (211) noted that low individual SES corresponded to poor prognosis with statistically significant (p<0.001) differences for 2 year OS. At the individual level the OS went from 0.59 for low SES patients compared to 0.74 for higher SES patients. For neighbourhood level SES the OS was 0.59 weighed against 0.70 for low versus higher SES groups.

Specific to the United States, insurance status was also found to have an impact on survival with privately insured patients having better survival. (367) The odds of presenting with advanced tumours were high for patients on Medicaid or uninsured and they were also more likely to present with nodal disease with larynx cancer having odds of worst overall survival at 6.97 for advanced stage and 4.18 for nodal disease. (367)

A number of studies, (360, 368, 369) demonstrated a link between education and survival, and this link remained after controlling for the confounding effect of gender. (369) An association between education and survival was shown in larynx cancer particularly in males with evidence that this form of HNC had a better prognostic outlook, (370) although improved survival in larynx cancer was not confirmed elsewhere in this review. Evidence of high social inequality amongst men for cancers of the larynx, mouth and pharynx were observed in Spain between the years 2001 to 2003. (369)

Being educated to a higher level was linked to improved survival, whereby post secondary educated p16-positive oropharyngeal cancer (OPC) patients had a hazard of death of 0.93 ($p=0.03$). The survival estimates in oral cavity cancer showed a hazard of 0.95 but this was not statistically significant but may have clinical relevance. (360) The odds of survival for college/technical school level patients versus education less than college level showed poor survival with a risk of 1.30 ($p=0.0056$). (368) The higher the educational attainment, the better the chance of survival with case fatality ratios improving from 1.12 for middle school level to 0.78 and 0.70 ($p=0.401$) for high school and university educated respectively for mouth and pharynx cancer, although no clear relationship was evident for larynx cancer. (370)

Differences in survival by education level were shown for both sexes. Uneducated males had decreased survival with an increased risk of death of 24% compared to 14.8% for university educated counterparts, with rates in females in corresponding categories at 33% and 9.7% respectively. (369) This survival trend was also evident in mouth and pharynx cancer, although

trends in females were more stable. (371) Males had consistently worse survival at 1 year, 3 years and 5 years (p=0.05) compared to females (356) and being educated better than elementary school level was associated with improved survival with a 30% reduction in risk. (356) Occupation was a significant predictor of survival. (356, 371, 372) Professional/managerial level patients were generally found to have better survival in one of the three studies (356), which found that this group had a reduced likelihood of death of 20%. The findings of Wong *et al* (372) were less definitive with five year survival in the unskilled group at 70.57% which was marginally better than that of the professional/managerial group with a rate of 65.56% (log rank X_2= 10.74, p=0.005), with this result remaining significant after adjusting for stage. Unemployment decreased the prospects of survival in patients with nasopharyngeal cancer (NPC) as the risk of death increased to 3.71 (p=0.01) (360).

2.9. Discussion

The literature search identified three studies that fulfilled the inclusion criteria fully and sixty-nine studies that attempted one or the other aspects of the research question. Sample sizes varied between studies and aims of the studies were equally heterogeneous. HNC is a particularly challenging area of cancer care and treatment due to the debilitating effects of both the disease process itself and the treatments (therapies) used. The heterogeneity of the subtypes of HNC may not make for easy comparison e.g. comorbidity in oral cancer cannot have the same prognostic impact as comorbidity in cancer of the parotid gland or a mixed HNC population. In addition there have been changes in treatment guidelines with both chemotherapy and radiotherapy now used in combination to ensure successful intervention. (373) These treatments have their associated effects notwithstanding the exacerbation of these treatment effects from patient related factors such as comorbidities, functioning status and concomitant risky behaviours such as smoking and drinking (which affect treatment efficacy). (180)

The poor survival in patients with comorbidities indicates both an additive and multiplicative relationship due to the multi-factorial pathology presented when HNC occurs alongside other medical conditions. The level of complexity poses key challenges to professionals as special attention should be paid to the possibility of treatment interactions due to the clustering of illness as well as the cumulative effects of both the index disease and comorbidity. (98) Comorbidity indices offer some method of assessment although there is variation in the information collected and how comorbidity severity is aggregated. Emphasis is placed on life threatening disease due their effects on survival outcomes e.g. arrhythmias and congestive heart failure (heart disease), chronic obstructive pulmonary disease, insulin dependent diabetes, liver disease, renal disease and gastrointestinal ailments. This was confirmed in a retrospective analysis of 1904 patients in the USA (374) when researchers found that comorbidities had an important and negative impact on survival, however this study was not included in this review as it did not give data on survival rates.

Although SES has been measured differently in the studies included in this review, there is a clear association with survival. Other SES factors that influenced early identification of cancer symptoms and resultantly cancer stage at diagnosis include level of education and income. Both these factors are associated with a lack of awareness of symptoms. (375, 376) Consequently this impacts survival prospects as late symptom identification leads to late presentation and consequently late diagnosis with more advanced tumours. (184, 377)

As described by Louwman *et al* (135), this analysis cannot decipher whether these survival differences are due to variation in exposure to risk factors as good education does not always equate to a good income. Education has been shown to have a protective effect (378) as it is has been demonstrated that well educated patients are more likely to notice any changes to their health status which may result in earlier diagnosis of localised disease which can result in the better survival outcomes. Hart *et al* posited the view that poor patients were more likely to die

from cancer than the rich, which has been shown in this review. (73) Although it is not clear whether this was due to late presentation or excessive exposure to poor lifestyle behaviours such as alcohol consumption, poor diet and tobacco smoking. (74) These patients from deprived backgrounds may be more vulnerable due to poorer health but knowledge of health promoting behaviours was lacking which may be responsible for the disparities found in this study. The socioeconomic difference in survival is explained by the excess mortality that is seen in this group and evidenced in this review.

Consideration should be to the contribution of other mitigating factors are involved in determining survival by SES. These may include factors such as:

- Medical
    - primary care,
    - speciality care,
    - access/use of services,
    - dental health services,
    - emergency services
- Behavioural
    - smoking,
    - drinking
    - health seeking behaviour
    - public health
    - symptom awareness/screening.

SES has been shown to have influence on the incidence of head and neck cancer but the exact types of social disparities that encompass SES had not been fully explored in SES prior to this review. As most HNC patients present with advanced disease, (172) prognostic factors such as comorbidity and SES negatively compound survival. This accumulation of competing disease has

a definitive effect on survival increasing risk of death by at least 1.5times when comparing patients with and without comorbidity, with worse outcomes for comorbidity severity. (139, 147, 153) The use of chemotherapy and loco regional treatment has been shown to demonstrate a survival advantage of 4% over 5 years but due to complications such as comorbidity, chemotherapy cannot always be used which nullifies the survival benefit. (379) It is apparent here that the more comorbidities a patient has, and the more severe the comorbidities are, the worse the survival prospects. (99, 153, 380) Diabetes has been shown to negatively impact survival which corresponds with evidence from Meyerhadt *et al* who found similar evidence in patients with colon cancer although in their case there was a clear biological interaction responsible for the reduction in disease free survival. (381)

Since the landmark study by Kogevinas *et al (382)*,followed up by the HN5000 paper it has been clear that socioeconomic gradients in cancer survival exist and have widened considerably in the last two to three decades. This is especially relevant to HNC as data shows that although year on year survival is improving, there are marked disparities in survival between deprived and affluent patients. A review of the two prognostic factors namely deprivation and comorbidity in HNC has not been attempted previously. Woods *et al* (129) previously reviewed the origins of socioeconomic inequalities in cancer which provided useful background information as it was deemed ineligible for inclusion into the review. Also work conducted by Munro *et al* (145) brought these two issues to prominence.

HNC is a cancer commonly occurring in the elderly, (65+) and it has been found to frequently occur in patients from deprived backgrounds hence the need to examine the prognostic role and contribution of both these factors in relation to HNC. There is a higher prevalence of underlying modifiable risk factors in lower SES groups which may point to the health inequalities apparent in HNC. It is clear from the evidence demonstrated here that if patients improve their lifestyle by reducing excessive drinking and smoking, this may influence survivorship in those that do

develop the disease, whilst also minimising the risk of developing a second malignancy if aetiological risk factors are not modified, or even the recurrence of the index cancer. (383)

The influence of HPV has to be considered as so far the literature shows that although HPV strains 16 and 18 are responsible for oropharyngeal cancer, (42, 55, 59, 60, 231, 384, 385) they have also been shown to have a protective effect with better survival for HPV-positive patients compared to HPV-negative patients. (386) It is not clear whether a socioeconomic effect is at play here, or whether HPV-positive HNCs have a social patterning as the deprived are diagnosed more frequently with HPV-negative cancers.

2.9.1. Strengths and Limitations of the review

Information used for the purpose of this review was obtained from research studies that used disparate methods, data collection and analysis. Some studies used different summary statistics such as cause specific survival and overall survival or both while others failed to report adequately to formulate meaningful conclusions.

The publication languages used were limited meaning that other potentially useful studies may have been overlooked, although efforts were made to identify studies from languages other than English and to translate them. Although the principal researcher used reproducible methods, the quality assessment tool was neither validated nor published and hence may be prone to non-systematic bias. Also the rating of assessment questions using an adjectival scale was purely subjective posing another methodological flaw. Although this was controlled for by using three other reviewers for the quality assessment process, there remains a residual risk of bias.

As regards the prognostic importance of comorbidity, although this review has found that it does affect survival, it has not clarified exactly whether this relates to specific individual comorbid diseases or number of comorbidities. The only way to definitively assess comorbidity would be to do so with individual patient data in separate cohorts, but this was not feasible hence blanket

assumptions of prognostication had to be made at the expense of more accurate but impractical measurements.

HNC refers to tumours derived from a distinct group of primary sites, while the studies used for this review considered all HNCs; it is possible that due to aggregation of tumour sites, there was dilution of the effect of both comorbidity and SES on outcomes. This is because HNCs such as laryngeal cancer have better overall survival than hypopharyngeal cancer; hence the direction of the effect of these two prognostic factors may not be as clear as expected. (387)

Also the variability in the sample sizes of the primary studies introduced heterogeneity into the review which may affect the overall estimates of survival. The only way to overcome this in future may be to use data from cancer registries that includes information on comorbidity status; on a single HNC to get more accurate survival estimates. Alongside this is the issue of the settings of the studies, as different countries or even regions within countries have different data collection methods. This is evidenced by the different data presented in the studies included in this review. There is a higher prevalence of underlying modifiable risk factors in lower SES groups (388) and the higher SES groups for HPV+ HNC (389), which may point to the health inequalities apparent in HNC. This may be due to the fact that HPV+ cancers are rarely clear cut and are independent of smoking and alcohol in their aetiology. Additionally, these HPV+ HNCs occur in younger patients who are known to have high number of oral sex partners which may point to the other forms of HNC occurring in older patients. The evidence suggests that improvements in health behaviours should theoretically reduce the incidence of HNC, improve outcomes and reduce the risk of developing a second malignancy.

There is evidence from the literature that there is a complexity in the relationship between health behaviour effects on HPV+ HNC and SES, (388) (384) hence improving health behaviours may not be enough. Patients from low SES backgrounds and those with comorbid disease may benefit from risk stratified care; therefore it is imperative that the systematic assessment and recording

of comorbidity status becomes standard practice; so that the influence of comorbidity is acknowledged making opportunities for further investigation easier. It may help for patients to improve their lifestyle by reducing excessive drinking and smoking, this may influence survivorship in those that do develop HPV-negative disease, as the findings of the HPV-related HNCs show that HPV reduces the risk of progression or recurrence of HNC and improves outcomes. (29, 30, 50, 59, 67, 68, 390-397)

It would have been ideal to conduct a focused review using the three studies; however this was not possible due to disparate findings between them. The Danish study (365) found that with each incremental level of comorbidity, the hazard of dying increased but the effect of SES, measured by social class did not demonstrate an association with survival. Of the other two American studies, the first showed that patients with comorbidity and classified as self-pay/no charge/others had greater odds of dying compared to those with private insurance ($P<0.02$). (340) The second study reported advanced comorbidity was indicative of poor survival for all patients with statistically significant hazard ratios of 1.436 ($p=0.0005$) for HNC-specific survival and 1.482 for overall survival ($p<0.0001$). (341) Although there was evidence demonstrating that comorbidity was linked to poor prognosis even after controlling for confounders; and that patients who were uninsured or on Medicaid had worse survival when compared to privately insured patients, the results were not generalisable. No meaningful assertions could be made based on two studies from the same country as measurement methods for SES are different therefore I could not make meaningful conclusions from these studies. In essence despite the findings of the three studies being useful in informing practice, the extent to which research findings can be applied to settings other than that in which they were originally tested was limited hence the decision to include the studies that focused on either comorbidity or SES.

This review aimed to ascertain the prognostic importance of both comorbidity and SES in HNC patients. The heterogenous measurement of both factors made the generalisability of findings

difficult. Although some efforts at minimising this were made through use of statistical aggregation through the meta-analysis, this had to be broken down to separate analyses for the two comorbidity indices, ACE-27 and CCI. The main shortcoming from relying on data from comorbidity indices is that although these indices are efficient at collecting comorbidity information, they have inherent biases emanating from the limited number of conditions that are used to calculate comorbidity. It was unclear whether the comorbidities focused on within the different indices had prognostic importance in HNC therefore validity of these meta-analysis and narrative synthesis findings was limited.

It would seem that in addition to the systematic review and meta-analysis, which uses combined statistical effects, then furthermore a future method would be to conduct a descriptive review of what is known about comorbidity and SES within the context of HNC in a cohort of patients to attempt to untangle the complexity of these two prognostic factors using one of the theories about health and health behaviour such as the salutogenic model, particularly of relevance being the concept of sense of coherence discovered by Antonovsky (398) which is a way of distinguishing those external factors that all combine in a multiplicative manner to cause premature death. This would be a worth investigating within the context of HNC due to the specific challenges of the patient complexity posed by the additional prognostic factors of comorbidity and SES play a significant role in determining survival outcomes.

Taking an additional approach to the statistical systematic review by using the prospective cohort analysis would also enhance findings. This method is ideal in that it would utilise patient factors elicited using the salutogenic sense of coherence alongside the HNC diagnosis which would go a long way in allowing researchers to get a better understanding of the complex interplay between SES and comorbidity in determining HNC survival.

2.10. Conclusions

The evidence presented in this review demonstrates that comorbidity and deprivation are associated with poor survival in HNC patients although exactly how both factors contribute to this could not be definitively elicited. Of particular importance are that severity of comorbidity and greater numbers of comorbid illnesses are indicative of poor prognosis. SES as determined by low income or low educational attainment was also implicated as being associated with poor survival for patients in these categories. This matches the social patterning of the main aetiological risk factors, smoking and alcohol drinking; behaviours which have been demonstrated to cause and contribute to HNC. Although it was difficult to conduct a direct comparison between studies, this review has added rich data to the complexity of the clinical picture presented by patients with HNC. Ensuring better survival of patients with HNC is not dependent solely on choice of treatment but other factors such as comorbidity and deprivation have to be taken into account.

2.11. Chapter summary

This chapter described the systematic review process from the literature search, article review and retrieval of full text. Once relevant articles were selected as per the inclusion criteria, these were read, assessed for methodological quality and their data abstracted. An analysis of the included studies was carried with narrative synthesis of all SES studies and those comorbidity studies that had heterogenous measurement methods. A meta-analysis of the comorbidity studies also found an association between comorbidity severity and reduced survival. The comorbidity and SES studies found that worsening severity of comorbidity and low SES were linked to poor survival. Better educational attainment and high incomes were linked to improved survival. The next chapter will describe in detail how the methodological quality assessment tool that was used to appraise the quality of the included studies was developed, including the literature review used to devise the initial draft. A description of the pilot testing of the quality

assessment tool and the ensuing refinement that was conducted until a final quality assessment tool for prognosis studies was completed.

Chapter 3

3.1. Developing a methodological quality assessment tool

3.1.1. Chapter outline

This chapter introduces the development of the quality assessment (QA) tool which the systematic review reported in the chapter 2 required to conduct an assessment of the methodological quality of studies identified as relevant for inclusion. The principal aim of this chapter was to develop and validate a tool as a proposed gold standard approach for the methodological assessment of survival studies for use in the systematic review. As the critical appraisal and assessment of methodological rigour was found to pose a major challenge for the observational studies on survival such as the cohort studies that were identified in the systematic review process. As the methodological (QA) of such studies was an essential component of this review process, this led to the development of the first iteration of a (QA) tool. Following pilot testing and assessment of content and face validity, a modified version of the tool for survival studies to assess the quality of observational survival studies which paid particular attention to study design, adjustment for censoring and multivariate analysis. This tool was used to quality assess the included observational studies to be used within the systematic review. It introduced the pre-existing empirical evidence of assessing methodological rigour i.e. checklists and research studies and will provide a rationale for the creation of the QA tool.

3.1.2. Recap of the systematic review process

A systematic review has been defined as a review of the literature that focuses on answering a research question by identifying, appraising, and synthesizing all available relevant evidence.(195) It is important that the research evidence used is both relevant and trustworthy. (399) Tools evaluating the quality of primary research evidence for systematic reviews have been formulated

which employ critical appraisal and trustworthiness rating methods. Although quality assessment (QA) in systematic reviews was pioneered in randomised controlled studies, (RCTs) (400) it was asserted that, "assessing methodological quality is considered essential in deciding what investigations should be included in research syntheses and in detecting potential sources of bias in results."(401, 402) Therefore it has become good practice to assess quality in both experimental and observational study designs.

3.2. Background

There is an increasing volume of literature that focuses on determinants of survival outcomes but despite the number of such studies being published, there has not been a corresponding plethora of literature on methods to assess the quality of survival studies. Although guidelines exist that explain methods for the reporting of observational studies such as STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) (403) and Meta-analysis of observational studies in epidemiology MOOSE (198), there as yet does not appear to be guidance on the conduct of QA and the corresponding QA tools for use in a systematic review of survival studies.

A synthesis of robust empirical evidence is required in order to carry out systematic reviews of survival studies efficiently, using critical appraisal and the assessment of susceptibility to bias of the medical literature. (218, 400, 404) Survival studies are especially problematic as there is no gold standard or routinely used tools to assess the validity of said survival studies to warrant their inclusion in systematic reviews. (202) Overlooking the potential methodological flaws of included primary survival studies reduces both the internal and external validity of a systematic review; as this may introduce bias into the study resulting in flawed findings. (405) Systematic reviews of survival studies are generally quite complex to undertake as the methods are not as yet standardised unlike in the case of therapeutic and diagnostic reviews.

As different methodological components such as quality of reporting and potential bias all contribute to the quality of a systematic review, (406) it is essential that all these components that could lead to these shortcoming are accounted for by use of a QA tool. Survival studies of prognostic variables are essentially different from other observational studies as they determine how influential a prognostic factor is in determining the survival prospects of the target population. Survival studies allow for the calculation of time to event data using various statistics such as life tables, Kaplan-Meier, Log rank test and Cox Proportional Hazards Regression. The unique features of survival studies mean that the criteria required for QA of these studies differ significantly from those required for studies on evaluations of interventions. There is also a need for QA using a standardized approach rather than through use of an adapted tool which can introduce a biased assessment of quality, (407) as the tool is not meant to critically appraise survival studies.

3.3.1. Initial approach to Quality Assessment

As discussed in Chapter 2, the McMaster University Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies was not fit for purpose as it was more geared towards intervention studies. Another QA tool developed by the University of Montreal (217) was considered more suitable for a clinician. Especially of note is the observation that there is no identified 'gold standard validated tool for reviewing the quality of survival studies. (196, 408, 409) Consideration of a review of the literature on critical appraisal pointed to two tools that were potentially eligible for use either based on their own merit or with minor adjustments. (218) It is important to emphasise that the word 'quality' that is used to define critical appraisal and assessment of methodological quality, does not refer to the quality of reporting but rather the methods utilised within the conduct and analysis of research to make certain that the research study is free of bias. (218)

In spite of the modest number of tools developed for performing the assessment of observational studies, specific ones concentrating on prognosis were found to be unsuitable. (219, 405, 410-412) Although the checklists for the assessment of prognosis exist, (217, 219, 411) none of these tools have been systematically developed for use in systematic reviews of survival studies. Also they have not been validated despite similarities regarding the items they assess. It would appear that use of any of these would be dependent on researcher preference rather than one specific being classified as superior or more relevant. Unfortunately there was no evidence of, "analytical evaluations of the quality of the study" as described by Katrak *et al*, (413) i.e. these tools should have been published to demonstrate the empirical basis of their validity but this was not the case.

One potentially useful critical appraisal tool (411) was found by Sanderson *et al* in their review of critical appraisal instruments. (218) However, this tool proved inadequate in providing a complete and concise critical appraisal and QA of the included studies. (217, 219, 220) Assessing the quality of evidence from survival studies requires a tool that is specific to this purpose. The aim of this project was to develop and evaluate an evidence based QA tool to be used for the methodological assessment of survival studies included in a systematic review.

At this point it is important to clarify why this study is not developing a QA tool for prognosis studies instead it is focused on survival studies. Prognostic studies were defined by Carneiro (410) as, "cohort studies based on groups of subjects exposed to a suspected causative factor, but without evidence of disease, which have prospective comparison with an disease-free group, but without exposure to the cause), or case control studies (in which patients with a particular disease are compared to subjects without the disease to determine possible links between the exposure to a given factor and the appearance of the disease)." This project defines survival studies as observational studies that assess the effect of two factors; comorbidity and SES on survival or risk of mortality. The similarities within the critical appraisal approach is in the

assessment of methodological validity, however the remaining evaluation of how the clinical study affects the prognosis of an individual is not covered within the context of the survival studies.

3.3.2. Research objective

Aim: To devise a QA tool of observational (survival) studies for use in a systematic review on the effect of comorbidity and SES on HNC survival.

3.4.1. Literature search

The following search terms were initially used:

- study quality assessment;
- critical appraisal,
- quality appraisal checklist,
- methodological quality assessment;
- and evaluation of study quality.

Where possible, all terms were obtained from title, abstract, keyword, full text, with truncation used where possible to capture variation in the terminology, spellings etc. Due to the poor specificity and sensitivity of these search terms, the search was modified to use the search below:

1.	Quality assessment$	35 779
2.	Methodological quality	21 879
3.	Quality appraisal	1 190
4.	Quality rating	2 425

5.	Critical appraisal	19 049
6.	Susceptibility to bias	431
7.	Quality appraisal tool$	61
8.	Quality appraisal checklist	18
9.	Critical appraisal checklist	100
10.	Critical appraisal tool	196
11.	Quality assessment tool	858
12.	/OR 1-11	73 936
13.	Prognosis stud$	4 425
14.	Survival stud$	23 085
15.	Studies of prognosis	1 433
16.	13 OR 14 OR 15	400
17.	Remove duplicates	318

From this initial search strategy; a search which was conducted in MEDLINE via Ovid, EMBASE, Journals@Ovid Full text, and NHS Scotland Journals@Ovid from inception till March 2012.

3.4.2. Inclusion criteria

Articles were included if they made reference to a tool that described methods for assessing quality of observational studies on survival or prognosis. Abstracts were scrutinized for suitability before obtaining the full text of all relevant articles. Seven articles were found to be relevant to studies of prognosis. (202, 203, 221, 223, 410, 412, 414) There was no date limit on the search. One researcher (EM) conducted the literature search, titles and abstracts of all articles were assessed for inclusion/exclusion by two independent reviewers (EM and CM) and consensus for inclusion was reached through discussion. Articles were retrieved in full text for inclusion in the study. Published articles were included if they provided evidence of measurement and/or practical

properties for multi-item quality assessment tools assessing survival or prognosis in patients with chronic disease.

3.4.3. Specific inclusion criteria for generic and disease-specific tools

- The instrument had to be patient-reported
- Published evidence of measurement reliability, validity or responsiveness following completion in a specified patient population
- The instrument had to be recommended for use with patients with chronic disease
- The instrument provided English-language versions for use among adult patients regardless of geographic setting.
- Evidence available from English language publications, and quality tool evaluations conducted in populations within UK, South and North America.

3.4.4. Exclusion criteria

- Quality assessment instruments that were not published in full, or were not in English, were excluded.
- Tools that were used for appraisal of diagnostic instruments and interventions were also excluded. Clinician-assessed tools which have narrowly focused or vague questions.
- Single-item tools to be excluded as well as tools without empirical evidence of measurement properties.

3.5.1. Developing a methodological quality assessment tool

Although survival is a specific field within medicine, tools to assess quality in this area should not be restricted to design specific tools. It was decided that a more generic tool would be ideal as study designs usually utilised in survival studies are prospective and retrospective. (415, 416) Due

to the difficulties faced in obtaining a validated quality assessment tool on survival studies, following discussions between the review team (EM and FM), the decision was made to devise a tool for use in this review. In developing the tool, special attention was paid to criteria developed by Clarke and Oxman (417) with the criteria of particular interest indicated with an asterisk (*).

1. Study aims and objectives *
2. Methodology used
3. Sample selection *
4. Methods of randomisation and allocation blinding
5. Attrition *
6. Blinding
7. Outcome measurement characteristics *
8. Intervention or exposure details
9. Method of data analyses *
10. Potential sources of bias *
11. Issues of external validity

An initial draft of the QA tool was based on empirical work conducted by different researchers, (202, 217, 221, 222) and adapted into a tool. Right from the outset, it was determined that both prospective and retrospective studies would be assessed as part of the review, despite retrospective studies having an inherent bias compared to their prospective counterparts. Prospective studies are more advantageous as they utilise an inception cohort i.e. a consecutive group of patients at a similar well defined disease stage, but these types of studies are not always used. (204) Similarly case control studies were deemed unsuitable as they are prone to many biases as treatment effects are underestimated due to poor matching on factors related to allocation of intervention. (200, 418) Also the differences between cases and controls may

introduce non-systematic bias (203) while the use of retrospective studies is especially fraught with problems as accuracy of these is reliant on medical records. (204)

The principle characteristics of a robust quality assessment tool devised by the The Evidence for Policy and Practice Information (EPPI) Project were also considered in the QA tool formulation process. (419)

A- Trustworthiness of results judged by quality of a study within the accepted norms of methodological quality,
B- Appropriateness of study design for addressing the methodological relevance to the research question,
C- Appropriateness of focus of the research for answering the research question,
D- Judgement of overall weight of evidence based on A-C.

All these characteristics are integral parts of evidence based practice. (205) To minimise confusion or misinterpretation, it was decided to provide guidance of what to do with the results, (217, 411, 412) i.e. whether the QA tool would use a scoring system and an overall score with ratings to explain the overall methodological quality of the QA tool. Discussion resulted in the team deciding on the use of adjectival scores and/or weighting of results (420). The chosen adjectives were 'yes', 'no', 'partly' and 'unclear'. Weighting in quality appraisal is purely arbitrary and subjective hence this method was discarded before it could be explored further. (421) However the use of adjectival scores was considered with the caveat that it would encompass the consensus approach whereby the review of quality ratings was performed by 2 or more investigators.

From this discussion it was accepted that the aforementioned may not be enough to fully take into account possible shortcomings in the quality assessment tool development process. It was therefore decided to use the approach suggested by Streiner and Norman. (420) This was

adapted using evidence from research, (202-204, 223) to develop the tool. This used the following stages of development:

1. Devising the questions
2. Question/item selection
3. Assessment of face validity
4. Pilot testing of item reliability, consistency and construct validity
5. Generation of the modified tool

1. Devising the questions

The quality assessment tool was devised for use in systematic reviews of survival studies and it was not intended to be restricted by type of survival. It was intended to provide a consistent and reliable way of conducting the quality appraisal of survival studies. It had to be equally able to allow for different raters to reach similar rating scores for the same study. Another prerequisite was for the tool to be clear and concise allowing brief but simultaneously accurate objective quality assessment of primary studies of survival. The quality ratings were 'strong', 'moderate' and 'weak 'with scores of '3', '2', '1' and '0' dependent on the assessment question rating of 'yes', 'no', 'unclear', and 'can't tell' respectively. This was the simplest form of objective assessment and studies scoring the maximum score of 24 having the highest rating.

A review of quality assessment tools conducted by Sanderson *et al* (218) only found two studies that were mentioned as quality assessment tools of prognosis. (217, 411) Neither of these tools demonstrated how quality could be incorporated into a systematic review. The incorporation of a adjectival scale (420), i.e. "…to give the rater a clear, unequivocal conception of the continuum along which he is to evaluate objects…" (420) in order to distinguish between high and low quality studies. In spite of the evidence against the use of quality scores, (422) this tool used quality scoring as a feature as all studies in the systematic review were reported on whether their rating showed high/low quality. This was a convenient way to include measures of quality in a

systematic review. Whiting *et al* (406) in their systematic review did not recommend the use of quality scores. However, as reviews of primary survival studies are usually of poor quality, (418, 423) it was decided that use of quality scoring in this review would enhance the reliability of summary measures to be used in both the narrative synthesis and meta-analysis. This method resulted in a tool that could be adapted for use in other systematic reviews of survival as a criterion for inclusion of primary studies. It was also possible to use the quality criteria for the narrative discussion of findings which can be presented in summary tables.

2. Question selection

This was conducted initially using questions taken from the tools developed by the universities at McMaster (424)and Montreal (217), as well as the Health Evidence Bulletin in Wales. (219) Items were also modified using review articles(202, 223) which incorporated items similar to those detailed in the tools used by the author alongside evidence from research articles by Marx and Marx (221), Laupacis *et al*(203), Carneiro (410), and Darzins and Smith. (412) This was condensed into 14 questions as per the tool below.

3. Initial assessment of face validity

All the items for possible inclusion were presented to a research interest group (membership is listed in table 10). The aims of the tool within the context of a systematic review were explained as were the methods for developing the quality assessment questions. Comments and suggestions for modifications to the tool were encouraged.

b) Face validity Round 2

The results of the research interest group meeting were used to modify the tool from initially one with 14 questions reduced to 8 questions. Thereafter the tool was pilot tested on 30 studies (see Table 11). Following this it was found that the tool had a bias towards rating all studies as strong

despite methodological weaknesses in both the conduct and the reporting of the pilot studies using basic critical appraisal skills. (196)

4. Content validation

This process was used to fine tune items for inclusion in the quality assessment (QA) tool. Evidence from Centre for Evidence based Medicine (411) and NICE (425) were used to refine the tool appropriately. This was done to improve the consistency and reliability of the tool so that if QA was carried out by more than one researcher, there would be good consensus on the quality ratings.

The completed tool was presented to a group of research experts for discussion and peer review group membership is presented in Table 10. The experts were asked to make judgements on the specified quality appraisal questions part of the instrument to measure the methodological quality of survival studies. Ideally the group of experts for validity assessment have been made up of experts from the field of cancer survival, but it was felt that researchers with experience of conducting systematic reviews and also other forms of primary research would afford the best objective approach to assess the appropriateness of the content of the QA tool.

Table 9 Research Interest Group Membership

Initials and Designation	
CM – Thesis Supervisor	FS – Thesis Supervisor
ST – Clinical Trials Unit Coordinator	BG – Professor of Primary Care
AG – Research Fellow	BS – Professor of Population Science
DM – Discovery Fellow	DM – Senior Clinical Research Fellow
JB – Research Nurse	NT – Research Fellow
PD – Professor of Biostatistics and Epidemiology	SG – Lecturer in Medical Anthropology
VS – Clinical Academic Fellow	PD – Lead for Quality Improvement

Content validity of the tool appeared acceptable but issues such as the number of questions (content analysis) and time it may take to complete the tool were highlighted as initial drawbacks. The tool was reworked until the version dated 27 March 2012 was completed and a pilot QA of the 30 papers was conducted by the principal researcher (EM) (initially). The purpose of this was to assess whether the QA process was free from bias and fairly amenable to a systematic review approach, while assessing the internal and external validity of each article, and determining its importance within the context of this review.

3.5.2. Iterations of pilot QA compared to later QA

All the studies in the pilot quality assessment were assessed using the QA tool and data was extracted onto a form detailing the results for each study (see Table 11). The information presented by the study authors was taken at face value and used to assign a response to each of the fourteen assessment questions.

The QA process did not only demonstrate an inherent bias towards rating most papers as strong quality during the first pilot assessment, there were some outliers that were considered weak or moderate even though the way the research was conducted and reported merited a much higher quality rating. The two pilot processes are depicted in Table 10 showing the variations in methodological quality between the assessment tools.

Table 10 Comparison of QA between the MQA and Modified MQA for Survival Studies

Study information	MQA score and rating	Modified MQA score and rating
*Anandan *et al(354)*	24/28 Strong	13/24 Moderate
*Andersen *et al(365)*	25/28 Strong	16/24 Moderate
Arbes *et al(311)*	27/28 Strong	23/24 Strong
Booth *et al(426)*	18/28 Moderate	17/24 Moderate
Castro *et al(427)*	27/28 Strong	20/24 Strong
Chen *et al(161)*	25/28 Strong	19/24 Strong
*Chu *et al(360)*	8/28 Weak	23/24 Strong
*Chu *et al(362)*	26/28 Strong	17/24 Moderate
Coleman *et al(309)*	17/28 Moderate	16/24 Moderate
Datema *et al(330)*	27/28 Strong	21/24 Strong
*de Cassia Braga Ribiero *et al(140)*	24/28 Strong	15/24 Moderate
de Graeff *et al(361)*	26/28 Strong	22/24 Strong
*Hathaway *et al(428)*	26/28 Strong	11/24 Weak
*Konski *et al(368)*	28/28 Strong	16/24 Moderate
Kwok *et al(367)*	27/28 Strong	23/24 Strong
Liu *et al(337)*	28/28 Strong	23/24 Strong
Mackillop *et al(359)*	23/28 Strong	19/24 Strong
Mell *et al(339)*	28/28 Strong	21/24 Strong
*Menvielle *et al(371)*	21/28 Strong	15/24 Moderate
Piccirillo *et al(148)*	27/28 Strong	20/24 Strong
*Puigpinos *et al(369)*	17/28 Moderate	23/24 Strong
Rosso *et al(370)*	20/28 Strong	18/24 Strong
Soares *et al(334)*	23/28 Strong	22/24 Strong
Tanvetyanon *et al(333)*	24/28 Strong	22/24 Strong
Teppo *et al(290)*	24/28 Strong	21/24 Strong
Terhaard *et al(331)*	28/28 Strong	22/24 Strong
Warnakulasuriya *et al(357)*	27/28 Strong	22/24 Strong
Wong *et al(372)*	27/28 Strong	22/24 Strong
*Woodard *et al (351)*	21/28 Strong	16/24 Moderate
Yung *et al(150)*	28/28 Strong	19/24 Strong

*Indicates studies that showed a discrepancy in the quality ratings after the QA tool modification.

A paper examining the impact of socioeconomic status (SES) on survival (360) was found to be 'weak' although critical appraisal showed that this paper had reported robust research methods. This paper made the principal researcher question whether the quality assessment tool was asking the right questions to ascertain methodological quality. These questions appeared to be restricted to risk of bias assessment which mainly led to appraisal of internal validity of the studies without any regard as to how their internal validity measured up. A similar pattern was noted for eight other papers. (140, 351, 354, 362, 365, 368, 371, 428)

The first version of the QA tool appeared to focus more on the strength of the inference one may draw from the study findings. There was no scope as to how statistical conclusions of the study gave validity to the findings reported by the authors. This is an area that the principal researcher felt required to be addressed within the quality appraisal process. It was also important to focus on whether incompleteness in reporting had an influence on the analysis and interpretation of results. Therefore, the principal researcher following discussion with the thesis supervisor (CM) decided that it was essential to include this aspect of methodological quality within a modified tool.

Another shortcoming of the initial QA tool is that it was open to subjective interpretation as shown by variation on the results of the pilot appraisal as shown in Table 11. This is despite the pilot assessment was conducted by one person only. In reviewing the tool, it was decided that using a guide as to the interpretation of each question's meaning and the information sought would be the ideal approach to minimize bias and subjective variability of findings. This resulted in the QA process being handled by three separate individuals, EM (principal researcher), CM (thesis supervisor) and FM (fellow research student).

3.6.1. Results

The literature review found that a variety of sources existed for potential items to use in a quality rating tool for systematic reviews of survival studies. (202-204, 223)

3.6.2. The tool

The modified quality assessment tool for survival studies has a list of 8 questions which have the following answers "yes", "no", "partly", "can't tell". The tool is presented in the appendix, while a detailed description of each quality appraisal question and what each question is meant to elicit is also included.

The methodological quality assessment tool was revised using more rigorous research evidence. (202, 203, 223, 411) until a final version (16 May 2012) was completed. Again this tool was presented to a research group for face and content validity. The group of research colleagues were consulted, as a part of the content validity assessment, to identify areas of omission and to suggest areas for improvement or modification. The comments were extremely encouraging with earlier shortcomings no longer an issue. Also to minimize the possibility of different interpretations of each appraisal question, a dictionary of the meaning of each question was devised to make this tool useful and adaptable for future projects. The subjective perceptions (face validity) of the panel of experts concluded that the tool was appropriate for measuring the quality of primary studies in a review of observational (survival) studies. A comparative pilot assessment was conducted and is depicted in Table 10.

Two reviewers, the researcher and a colleague with some research experience independently assessed each study then discussed their ratings together. Any disagreements were discussed and resolved by consensus agreement and final discussion with the dissertation supervisor as the third reviewer. Appendix A4 details the final tool with the corresponding guidance.

3.7. Discussion

This literature review produced an evidence based tool for the quality assessment of primary research on survival for use in systematic reviews. It is a simple but concise tool consisting of eight questions. It also includes a methods guide or dictionary to explain what each question relates to. It also includes an overall quality score which is useful for meta-analysis as any studies that were rated as "weak" can be excluded.

The face and content validity methods were used to formulate the final tool in conjunction with input from the group of researchers. The pilot testing of the tool both at inception and for the final draft was utilised to highlight any inconsistencies or biases in the type of questions used to

assess methodological quality. This resulted in a tool with strengths but in spite of this there are some limitations to it. The quality scores do not provide an objective assessment of the quality of a primary research study. (429) The choice for the methods of grading or calculating quality is purely arbitrary and as no weighting was allocated to be indicative of the relative importance of individual quality appraisal questions over others. (422) Despite these shortcomings this tool is robust as it is evidenced from the literature on how to use articles of prognosis (survival), and has been systematically developed using these same sources.

Although the review of the literature had found a few tools that appeared to have fulfilled some of the criteria which this study had sought to develop as part of the methods for the assessment of methodological quality of prognosis studies. Like the tools by the University of Montreal (217, 412), prognosis was addressed in the context of the clinical relevance of on an individual patient. As a result, the tool developed for this systematic review is a far superior approach as it can be applied to the clinical studies to assess whether both their conduct and results both possess a high quality in terms of internal and external validity.

3.8. Conclusions

According to our knowledge this is the first attempt at condensing all the guidance on critical appraisal of survival studies into a meaningful tool providing both direction and a way to assess the methodological quality of survival studies. This tool acts as a generic starting point for quality assessment of primary survival studies without being limited by study design or setting. The versatility of this methodological quality assessment tool means it could be used to do quality assessment of papers focused on other diseases. It is easily adaptable to any condition as the quality assessment questions help to identify methodological rigour in a primary research paper. This tool will help assess the methodological soundness of methods used in a primary study but this has to be approached with caution as poor reporting does not always equate to poorly conducted studies. It is envisaged that the development of the MOOSE guidelines (198) has

contributed to the improvement in the quality of reporting of observational research such as studies of survival. This should diminish the likelihood of well conducted but poorly reported studies being published in future. The development of this tool should hopefully enhance the standards of systematic reviews of primary survival studies.

3.9. Chapter summary

This chapter discussed the process used to devise a QA tool. This tool would be used to evaluate whether studies that were selected for inclusion in the systematic review used sound methodology. The literature searches and selection of articles that focused on survival (prognosis) was conducted with the final resulting from an amalgamation of key questions from various sources. The process of face and content validation as well as the pilot QA was conducted in order to refine the tool and ensue it was fit for purpose. The final tool was devised and used to appraise the methodological soundness of the 70 articles that were included in the systematic review presented in Chapter 2. The next chapter will describe the data linkage methods used to prepare administrative health data for use in the retrospective study on the survival outcomes of HNC patients from Tayside and Fife based on their comorbidity status and SES. As described in the systematic review (Chapter 2) an ideal follow up to this work was to attempt to validate the systematic review findings in a cohort of HNC patients. In order to conduct this analysis of the retrospective data, HNC patient data from Fife and Tayside which was available for this project had to be linked with routinely collected administrative data. This next chapter will describe the process of obtaining the patient data and preparing the data for analysis and linking it in order to verify whether the systematic review results were generalisable.

Chapter 4

4.1. Data linkage methods

4.1.1. Chapter Outline

This chapter will describe the methods used to link administrative health data sources into a meaningful dataset of HNC patients from Fife and Tayside. It gives a comprehensive description of the routine health datasets that are used in Scotland. This includes the hospital data, death statistics and cancer registry information on HNC diagnosis. A definition of the procedures for obtaining these data, cleaning and the methods of linking them into a dataset will be given. The number and how any inconsistencies and duplicates were removed will be defined, alongside the process of assigning comorbidity status using the selected indices and the matching of variables will also be described. The data linkage of routinely collected data and patient data to create a single record with all important variables such as age, gender, HNC type, disease stage, TNM, summary scores for ECI and CCI, as well as Scottish SIMD quintiles, and income and education domains will be conducted in preparation for statistical analysis of these data.

4.2. Routine healthcare datasets

Scotland has high quality routine healthcare data which have been collected over the last 40 years in mostly an electronic format and provide opportunities for record linkage. National Scottish datasets are maintained by Information Services Division (ISD) Scotland of the National Health Service (NHS). These data are collected from the point of birth until death using a unique patient identifier which the individual uses throughout the life course.

The unique patient identifier is known as the Community Health Index (CHI) number (430)which is a unique ten character identification number that has been in use in Tayside since the late 80s

and throughout Scotland over the last decade. It is made up of six digits from the date of birth (DOB); the next two digits are a unique identifier with the ninth digit representing gender, with an even number for females and an odd number for males. The tenth digit is a check sum for validation purposes.

A community prescribing database of prescriptions issued within the community is also kept. The information used in this database is obtained through GP issued prescriptions which are filled at a local pharmacy by the patient. The script is forwarded to the ISD Pharmacy Practice Division with the same information forwarded to the Health Informatics Centre (HIC) (431) regarding any Tayside and Fife prescriptions which are then entered onto the database. This service has been in place since 1989 and became fully operational in 1992.

The Scottish Morbidity Records (SMR) Database (432) covers all patients in Scotland, and relevant care episodes requiring admission to non-obstetric hospitals together with any cancer registration and corresponding death records. These records known as SMR are collected by local NHS Scotland Health Boards and collated at the ISD. This information is collected for planning, monitoring, costing and contracting of the health service. All SMR data for Tayside and Fife is available through HIC.

4.2.1. Types of SMR that is to be used in this study: -

- SMR01 (432)- admission to non-psychiatric care/non-obstetric hospital for inpatient stay or as a day case

Three databases spanning three time periods 1980-1995 (ICD 9 codes), 1996-1997 (ICD9 and 10 codes) and 1997 onwards (ICD 10 codes only). This study will use the SMR database from 1997 onwards which includes patient identifiers such as CHI No, ICD-10 codes and admission hospital. The International Statistical Classification of Diseases and related health problems (ICD-10) is the

10th revision of a medical classification list compiled by the World Health Organisation (WHO). (7) The ICD-10 codes are used to classify diseases and other health problems.

- SMR06 (432) or Cancer Registry

These data have been collected since 1958 at regional centres and was changed to a single national disease registration in 1997. The SMR06 gives information on all cancers as well as benign brain and spinal cord tumours. The data collected from the following sources is used to create the SMR06 record:-

1. SMR01,
2. Pathology,
3. Haematology,
4. Oncology,
5. Radiotherapy,
6. Prospective cancer audits and
7. General Registrar's Office (GRO) Scotland death records.

There is a legal obligation to record any death occurring within Scotland. This information is then collated by the GRO Scotland. (432) The cause of death has to be included as per the medical death certificate and this information has been mandatory since 2000. HIC has access to this death data with the CHI number being manually added based on name, date of birth and current address to allow data linkage.

The Scottish index of Multiple Deprivation (SIMD) (433) is a measure of deprivation that identifies small area concentrations of multiple deprivation across all of Scotland. It was designed to capture many aspects of deprivation in individual domains such as employment, income,

education, health, access to services, crime and housing. Previous measures of deprivation used measures that came from the Census (e.g. people not owning a car, overcrowded housing and so on) but this information went out of date quite quickly. The advantage of the SIMD is that it uses small units of geography that can be aggregated up into larger areas e.g. councils, CHPs, health boards. It ranks the 6,505 datazones in Scotland from 1 being most deprived to 6,505 being the least deprived and it does this for each domain as well as giving an overall ranking which is a weighted sum of the seven domain scores. (433) The SIMD is aggregated into quintiles and deciles. The quintiles split the datazones into 5 groups, each containing 20% of Scotland's datazones, while deciles split the datazones into 10 groups, which each contain 10% of Scotland's datazones. The main disadvantage from use of the SIMD is that it is based on a patient's postcode

There are issues around the use of routinely collected data with evidence of both advantages and disadvantages.

4.2.2. Strengths and limitations of routine data

The strong points of routinely collected data include-

- These data are readily available
- Usually at low cost
- Useful for establishing baseline characteristics
- Useful in identification of cases for a case-control study
- Aid in the generation of aetiological hypothesis
- Help to derive the expected number of cases in a cohort study
- Useful as a source of ascertaining outcome in a cohort study

- Useful for examining disease trends over time and place

In terms of weaknesses, generally these data are prone to bias, measurement error and incompleteness as well as the following characteristics:

- not always up-to-date (dependent on when collected)
- lack of completeness (except census)
- some variables of interest may not be collected

4.2.3. Access to routine datasets

This was sought through submission of requests in the form of a study protocol and data analysis plan to the following two sources:

1. The NHS Tayside and NHS Fife Caldicott Guardians and their respective Research and Development Departments (R&D)to allow use of anonymised patient data for research purposes

2. The HIC data protection officer who ensures that all necessary permissions are in place and that data that is generated is anonymised before it is released for use by the researcher. The data are accessed only through a restricted database called a safe haven which is operated by HIC. The Scottish Government has defined a safe haven as, "a secure physical location that embraces standards of operation that ensure that confidential personal information is handled safely with appropriate levels of electronic security. It contains a computer but has no external devices with removal of any information from the safe haven strictly controlled by the HIC team.

4.3. Identifying the cohort

Once approval (See Appendix) was obtained from the relevant Caldicott Guardians, R&D departments and HIC, the data was forwarded to the principal researcher. The cohort was identified from two main sources: Fife patients were identified from records kept by the Head and Neck Cancer Nurse Specialist who had kept a record of all incident cancers that occurred since inception of her post in 1989. This resulted in Fife patients being identified as any individual with a diagnosis of HNC based on clinic notes, or who had a hospital discharge record (SMR01) with a code for HNC; or any individual with a HNC record (SMR06) in the Cancer registry who was a Fife resident; or anyone with a cause of death code of HNC in the GRO death records system.

Tayside patients were initially identified using a retrospective case note review of all HNC incident cases from the Tayside area from 1997 onwards. These patients were identified as HNC cases based on diagnostic records from Oral/Maxillofacial, Ear, Nose and Throat (ENT) and dentistry. This also encompassed patients with a hospital discharge record (SMR01) of HNC, or any Tayside resident whose Cancer registry record (SMR06) was coded for HNC, as well as anyone with a cause of death within the GRO death records coded as HNC.

All the additional data (SMR01 and SMR06) were requested from the HIC Data Protection Officer and matched to the unique patient identifier (PROCHI) and added to the project population.

As part of the information governance approval required for this project, HIC provided patient data that was anonymised meaning that there was no identifiable information within the dataset. The data was made available through the Safe Haven which is a secure access portal administered by the HIC team at University of Dundee. Safe haven access was obtained through submission and approval of a protocol and data analysis plan to the HIC.

4.4. Data linkage

Although the data for the Fife and Tayside HNC datasets were collected for research purposes, these were independent operations. Due to inconsistencies in the level of detail collected for the key variables; careful thought and planning was required to merge the data with the other routine data sources in order to create a meaningful HNC patient cohort. The analysis of the Tayside and Fife data was conducted separately as Tayside had small patient numbers while Fife had a larger cohort but with missing information, although combining the two cohorts would help elicit more meaningful results which would have greater validity and generalisability.

To ascertain that all the patients in both the Fife and Tayside cohorts had a diagnosis of HNC, diagnostic codes relating to HNC from the International Classification of Diseases 10th edition (ICD-10) (7) were cross matched against the SMR06 (432) Cancer Registry codes for both cohorts. The SMR01 (432) data was used to highlight any hospital discharges for concomitant disease other than the index disease, HNC. The diagnosis code was matched to key comorbidity conditions listed in the two indices of interest, the Charlson Comorbidity Index (99) and the Elixhauser Comorbidity Index (ECI). (103)

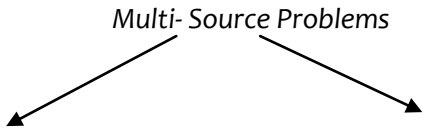
4.4.1. Data extraction

The anonymised dataset was allocated a unique identifier known as PROCHI to each patient record. The list of PROCHIs for both Fife and Tayside were matched against hospital discharge and cancer registry data. The GRO death records were used to identify any deaths and any corresponding causes of death for the specific individuals within the cohort. All the data i.e. SMR01, SMR06 and GRO death information were linked to make an individual patient record alongside other demographic information available in the amalgamated Fife and Tayside cohort.

4.4.2. Data cleaning overview

This process of data cleaning or data cleansing was carried out to aid the elimination of errors and improve the consistency of data found in the databases. The type of inconsistencies and errors that need to be dealt with include but are not limited to record duplication, incomplete or inaccurate entries. A process of record linkage was conducted, "a solution to the problem of recognizing those records in two files which represent identical persons, objects, or events (said to be matched)." (434) Therefore the information was closely reviewed for its quality and reliability with any inconsistencies, errors or inaccuracies addressed to improve data quality. (435) The classification of data quality problems in data sources (436) process is illustrated below.

Data quality problems



Schema level	*Instance level*
(Heterogeneous data models and Schema designs)	(Overlapping, contradicting and inconsistent data)
-Naming conflicts	-Inconsistent aggregating
-Structural conflicts	-Inconsistent timing

4.4.3 Data Cleaning Process

As determined by Maletic and Marcus (435) and Van den Broeck *et al* (437), there are three phases to the data cleansing process namely:

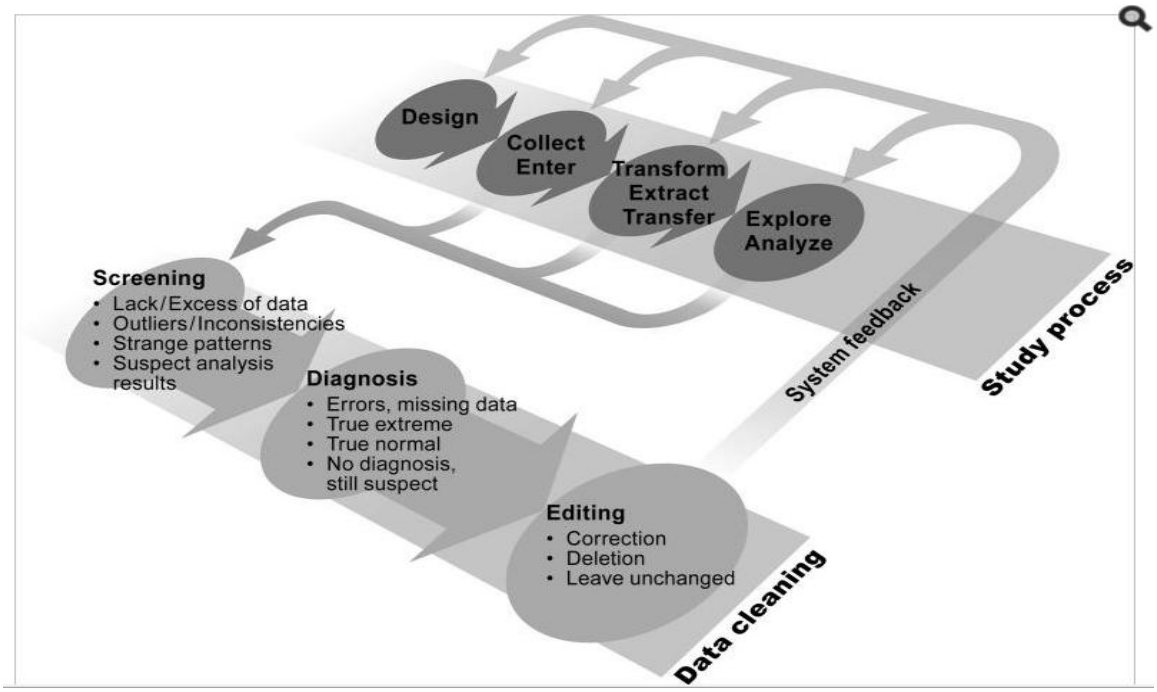
1) Definition and determination of error types through manual inspection of the data (screening),

2) Search and identification of error instances using verification to ensure that accurate error identification occurs (diagnosing),

3) Correction uncovered errors through data transformation (editing suspected abnormalities).

This process was conducted within Microsoft Access 2007 which allowed the researcher to manipulate the data while making the necessary adjustments and improvements. The data cleansing approach involved is depicted in the following diagram

Figure 12 Data cleaning approach



Source: Van den Broeck *et al* (437)

4.4.4. Data inconsistencies

Predefined queries were used to identify duplicate records. Three main datasets were initially identified as containing the pertinent data for the Fife cohort namely: all patients, episodes, and appointments. Due to the large volume of inconsistent data such as date of diagnosis and/or referral, diagnosis, and duration of appointments, the HNC Nurse Specialist who had collated all

the individual patient data assisted in clarifying any errors. Following this multiple entries for the same patient were removed as in most instances, a recurrence of HNC was recorded as a new cancer. Other inconsistencies that were apparent within the data were dealt with using the following methods:

a) Where there was evidence of 3 or more records for one patient, these records were reviewed. As all records had some useable information; the decision was made to merge them into 1 record i.e. row shift.
b) There were instances of duplicate patient records with the only variation being the date of diagnosis. The earliest date of diagnosis was taken while other dates were disregarded.
c) Duplicate records with identical information were also found and an arbitrary decision to keep only one such record was made using the first record as the default record for retention.

In order to reduce data inconsistencies a key review process of renaming variables was conducted to ensure consistent variable matching across the two datasets. Some data cleaning occurred during the analysis process as the importance of some variables only became apparent at this stage. Column shift was also evident as data from one column was entered onto an adjacent column. Descriptive statistics using frequencies specifically to elicit maximum and minimum values for variables such as age to ensure that the data made sense. Final logic checks were also conducted to ensure that the data made sense. This was done using the baseline patient files and the routine data was then linked to this.

Once it was verified through individual record checking that data appeared to be clean, the dataset was truncated into a summarised version with only key variables of interest to the analysis. This reduced the cohort variables from 125 to 23 which was a more manageable number thereby also minimising potential errors in the subsequent analyses.

The research question sought to investigate whether deprived patients with comorbidities presented with advanced and experienced higher than average mortality risk. It was therefore necessary to conduct risk stratification based on the key explanatory variables, comorbidity and SES. The process of assigning relevant values for the two prognostic factors was the next stage of preparing the data for analysis.

4.5. Identification of explanatory variables

The cohort eligibility criteria were defined as any patient residing in Fife or Tayside with a diagnosis of HNC, regardless of clinical staging of the disease. There were no restrictions placed based on gender, race, and length of survival or age. The definition of the cohort will report results of the Fife patients, followed by the Tayside patients. Finally the analysis will describe the combined cohort of the Fife and Tayside patients in full detailing the pertinent demographic characteristics as well as any survival analysis and multiple imputation results obtained.

4.5.3. Other important variables

Age was also considered to be of particular importance in the context of HNC survival as empirical evidence has shown that the typical HNC patient is older, aged 50+ and presents with more advanced disease (58) therefore it was crucial to assess the influence of age. To simplify matters, age was divided into categories as follows: ≤40 years; 41-50 years; 51-60 years; 61-70 years and 71+. As HNC occurs predominantly in males with the ratio for incidence standing at 2:1 compared to female, gender was also considered an important explanatory variable. Likewise tumour characteristics have been known to affect prognosis therefore it was important to assess whether disease staging had an influence on survival. Unfortunately not all patients had stage of disease recorded which was particularly the case for patients from the Fife cohort.

4.5.4 Assigning comorbidity

In order to conduct the analysis adequately, the pre-existing conditions, or comorbidities for all the patients in the cohort had to be systematically stratified using the following method:

(1) The conditions, (if present) that each patient had were matched to the conditions for each of the two comorbidity indices,

(2) The comorbidity information was summarised into a score which amalgamated all the relevant conditions,

(3) In the case of the Charlson Comorbidity Index (CCI), this also included the addition of age related information to provide an age related comorbidity score.

The comorbidity data was presented as ICD-10 codes which were then translated into the relevant conditions based on previous work. (438-441)

4.5.5. Measures of comorbidity used

Comorbidity is known to affect the detection of disease, treatment options and prognosis; additionally it has known to be the cause and consequence of the index disease. In HNC most of the comorbidities share the same risk factors as the cancer itself; therefore comorbidity can act as an effect modifier compromising the internal and external validity of any study findings.

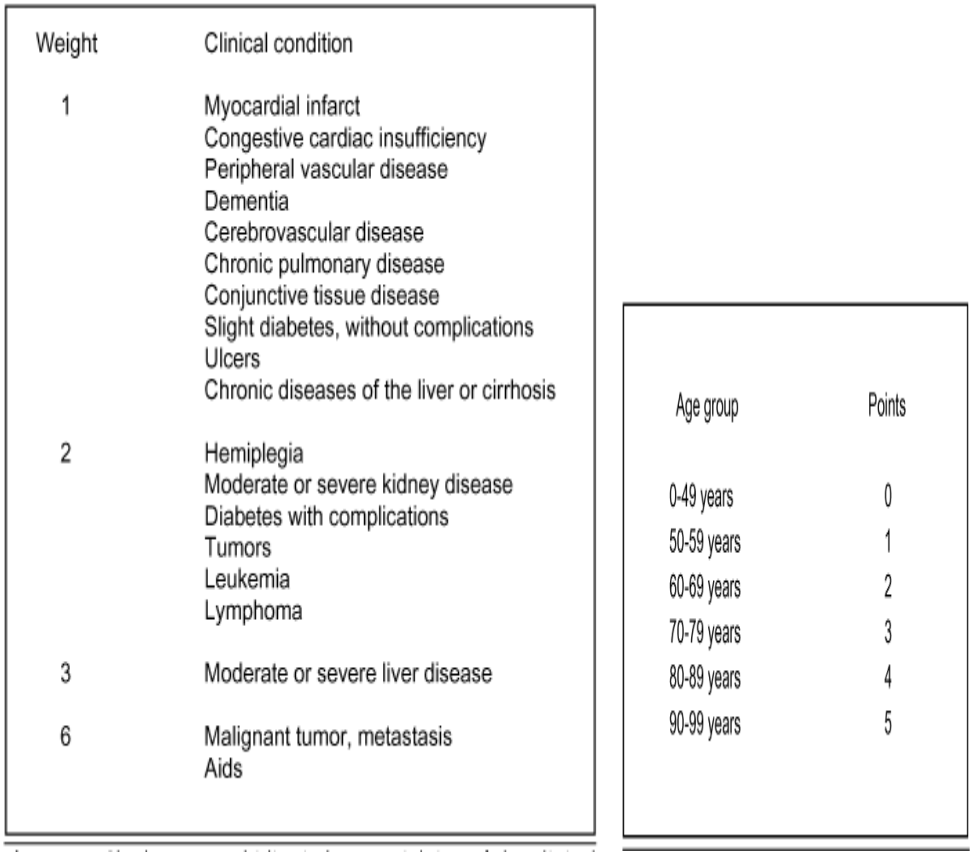
The choice of comorbidity measure was based on a number of decisions. The CCI was deemed ideal in conducting the analysis of the Fife and Tayside patient data as the findings from the systematic review pointed to the utility of both the ACE-27 and CCI to measure comorbidity. Initially it was envisaged that both indices would be used for the subsequent analyses. The ACE-27 index requires measurements such as blood pressure, creatinine levels, FEV1, alongside treatments such as blood transfusions of ≥6 units of blood, and diabetes medications, etc. As this information was not available, it was necessary to select an alternative comorbidity index to

provide meaningful comparison to the CCI. After reviewing indices used within HNC research, the index chosen was the van Walraven's modification of the Elixhauser index (ECI) as it provides a recent risk-adjustment model in comparison to the CCI. This scoring system for calculating ECI was selected for its superior ability to discriminate in-hospital mortality. Prior to settling on using the ECI and CCI, the principal investigator considered other comorbidity indices such as those mentioned within Chapter 1. The National Cancer Institute Index was not suitable because it considers ten coexisting conditions without providing the severity of these conditions. The Alcohol and Tobacco-related comorbidities index was too restrictive as it focuses only on comorbidities related to smoking and drinking and does not consider any other age-related conditions. The Washington University Head and Neck Cancer Index is derived from the ACE-27 therefore data collection would have been difficult due to the limitations pointed out with the ACE-27 index.

4.5.6. Comorbidity indices

The findings from the systematic review pointed to the usefulness of both the ACE-27 and CCI to measure comorbidity, hence both indices would have been ideal to use in the ensuing analyses The modified CCI (442) was selected over the initial version of the CCI (99) as it includes age to calculate a composite comorbidity score (see below). This was of particular importance in this study as age has significant influence both within the incidence and prognosis of HNC.

Figure 13 Age related CCI



Weight	Clinical condition
1	Myocardial infarct
	Congestive cardiac insufficiency
	Peripheral vascular disease
	Dementia
	Cerebrovascular disease
	Chronic pulmonary disease
	Conjunctive tissue disease
	Slight diabetes, without complications
	Ulcers
	Chronic diseases of the liver or cirrhosis
2	Hemiplegia
	Moderate or severe kidney disease
	Diabetes with complications
	Tumors
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Malignant tumor, metastasis
	Aids

Age group	Points
0-49 years	0
50-59 years	1
60-69 years	2
70-79 years	3
80-89 years	4
90-99 years	5

The rationale for use of the modified CCI (442) which incorporates age, was supported by its reputation as one of the most commonly used indices. The CCI was developed for the express purpose of prospectively predicting 1 year mortality among 600 patients with cardiovascular disease. As it has been used extensively in the field of cancer care and also in the systematic review (see Chapter 2), it was deemed an ideal comorbidity measure for use in this study.

The index chosen to compare against the CCI was the van Walraven (441) modification of the Elixhauser index (ECI). The original Elixhauser index (103) had been used extensively, but van Walraven *et al* modified it to calculate a single numeric score to summarise disease burden thereby representing comorbidity classification. The original Elixhauser Index provides a more recent risk-adjustment model in comparison to the CCI. It uses 30 conditions and also includes weight loss and obesity which are not included in the CCI. The ECI has been validated in other cancers namely, colorectal, (443, 444) cervical, (445) prostate, (446) oesophageal, lung, bladder,

pancreatic, colon and gastric. (447) van Walraven *et al* (441) developed their index by modelling in-hospital mortality with in-patient admission data from Ottawa Hospital from 1996–2008. This scoring system for calculating ECI was selected for its superior ability to discriminate in-hospital mortality using 15 conditions which is better than using the 30 individual comorbidities without a summary score.

Figure 14 Van Walraven's ECI

Elixhauser's Comorbidity Index van Walraven modification	
0	Hypertension - Diabetesuncomplicated - Diabetes, complicated – Hypothyroidism - Peptic ulcer disease, no bleeding - AIDS/HIV - Alcohol abuse - Psychosis
2	Peripheral vascular disorders
3	Chronic pulmonary disease – Coagulopathy - Rheumatoid arthritis/collagen vascular diseases
4	Pulmonary circulation disorders - Solid tumor without metastasis
5	Fluid and electrolyte disorders - Renal failure - Cardiac arrhythmias
6	Weight loss
	Neurodegenerative disorders
7	Congestive heart failure - Paralysis
9	Lymphoma
11	Liver disease
12	Metastatic cancer
-1	Valvular disease
-2	Blood loss anemia - Deficiency anemia
-3	Depression
-4	Obesity
-7	Drug abuse

The utility of the van Walraven method was confirmed for long-term cancer survival which is of relevance here as this is the main outcome measure of this study. (448) The scores according to the ECI method were categorized into the same groupings as to CCI to allow for comparison across the two comorbidity indices. As the classification of comorbidity varies depending on the index in use, the summary scores used in this project were not calculated through a simple count of conditions. The categories of mild and moderate comorbidity have different meanings dependent on the comorbidity measurement tool. A person's CCI summary score is the sum of

the weights assigned to each of the comorbid conditions alongside the age adjustment score. The assigned weights for each of the 19 conditions were derived from regression coefficients predicting survival in the initial development of the index. In the CCI, mild comorbidity refers to a score of 1, moderate comorbidity refers to a score of 2 and severe comorbidity is for an assigned score of 3 or more. (444) In the ACE-27 Index the assignment of comorbidity severity is based on the degree of organ decompensation and prognostic impact, i.e. the highest ranked single disease in different organ systems. A score of 1 meaning mild comorbidity is assigned when the comorbidities for a particular individual are all ranked as mild decompensation. Moderate comorbidity which is scored as 2 for condition causing mild decompensation but this only applies if only one condition is ranked as 2. If 2 or more conditions from different organ systems are found, then the comorbidity score is 3 meaning severe comorbidity. These categories indicate the overall prognostic impact which determines possible outcome taking into account the treatment selection and treatment management issues with the comorbidities and the index disease.

4.5.7. Defining Important Comorbidities

The entire burden of illness for a patient, as reflected in the information relevant to a hospitalization, can be divided into five separate concepts:

1. The primary reason for hospitalization, as reflected in the principal diagnosis;

2. The severity of the principal diagnosis;

3. Complications that result from the process of care;

4. Unimportant comorbidities or other conditions present on admission that have a trivial impact on resource use and outcomes; and

5. Important comorbidities or conditions present on admission that are not related directly to the main reason for hospitalization, but that increase the intensity of resources used or increase the likelihood of a poor outcome.

To conceptually identify important comorbidities, we attempted to exclude information that relates to the other aspects of a patient's condition, concepts 1 through 4 above.

4.6. Methods for variable matching

Table 11 Variable matching methods

Fife	Tayside	Matched variable
Sex	Gender	Sex
Age at time of presentation	Calculated age	Age
Tumour Node Metastasis → TNM	T N M → TNM	TNM
Staging	UICC stage	Stage
Diagnosis	Site of primary disease	HNC Type
Diagnoses date	Date of diagnostic histology	Date of diagnosis
Smoking	History of smoking	Smoking status
Alcohol consumption	History of drinking	Alcohol

4.6.1. Demographic characteristics

The demographic attributes of the population included age, sex, education level and income level measured using the Scottish SIMD. The data did not contain any information on factors such as marital status, ethnicity or occupation.

4.6.2. Tumour characteristics

Tumours were classified using the tumour-node-metastasis (TNM) system was adapted into stage according to the American Joint Committee on Cancer system as stages I, II, III and stage IV. (449)

4.6.3. Assigning alcohol status

Allocation of alcohol status was derived from guidance from the Institute of Alcohol studies which gave the calculated units of alcohol as follows:

$$\frac{Number\ of\ millimetres\ in\ drink\ x\ Alcohol\ by\ volume\%}{1000} = Number\ of\ units$$

These units were calculated for each patient where the data were available and each patient was placed into types of drinker groupings (see Table 12).

Table 12 Units and alcohol consumption guidelines

Drinker type	Men	Women
	Units per day	Units per day
Moderate	< 21	<14
Hazardous	21-50	14-35
Harmful	50+	35+

Source: Holmes *et al* (450)

4.6.4. Assigning smoking status

Smoking status was devised from reclassification of the smoking variable into 4 distinct categories based on methods developed by a team of pulmonologists led by Uzuner. (451)The categories were:

1. Never smoked
2. Ex smoker

3. Moderate smoker
4. Heavy smoker

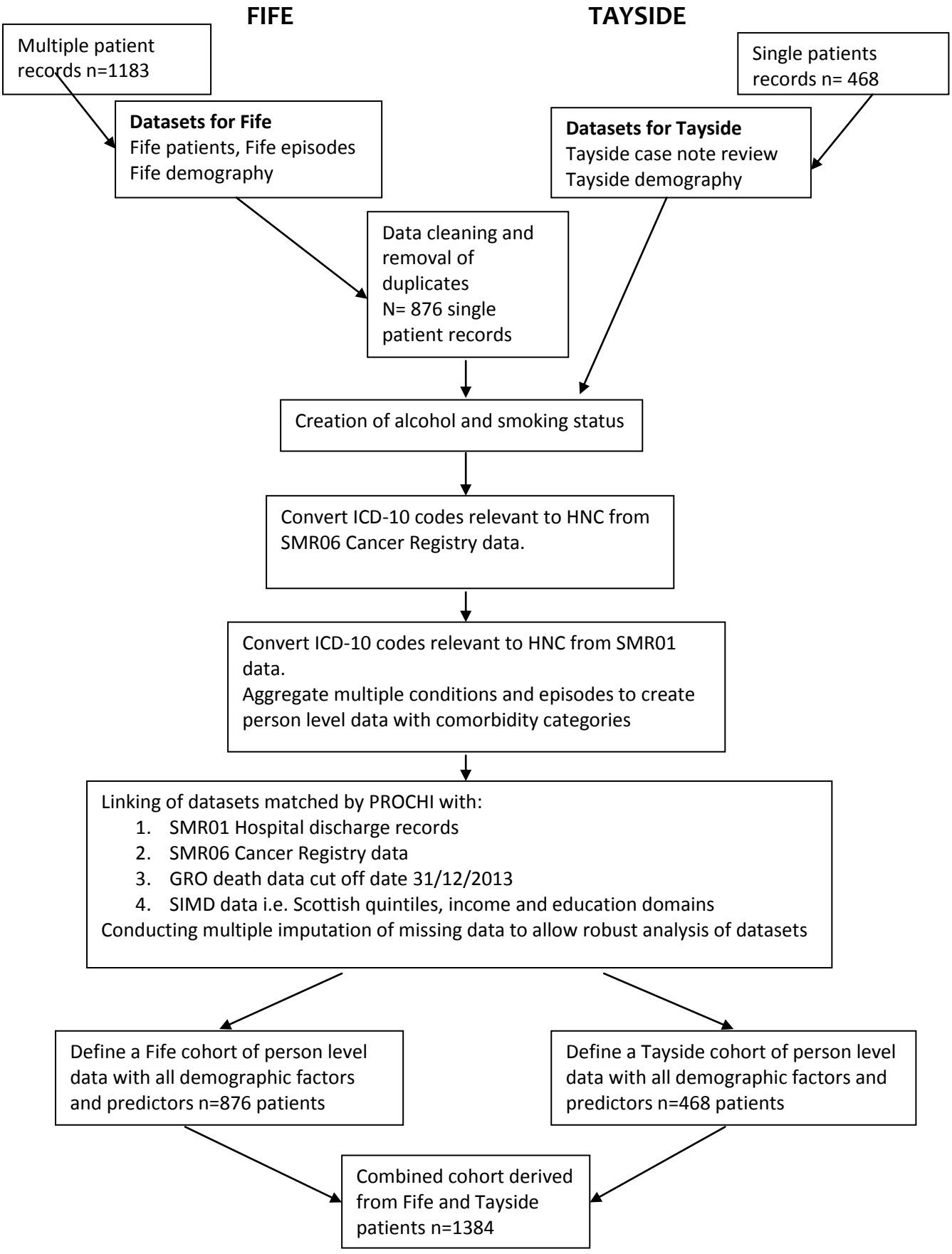
Where smoking was defined through quantity of tobacco smoked, it was estimated that 50g of tobacco made approximately 100 roll up cigarettes using a generous allocation of tobacco. (451) This meant that a person smoking approximately 14 of these cigarettes per day was deemed a moderate smoker. If quantity such as 15-20 cigarettes was given than the highest number was taken meaning this individual was classified as a heavy smoker. Therefore anything more than 20 cigarettes would be classified as a heavy smoker. This algorithm was deemed the most appropriate as it catered for patients with HNC.

4.7. Data linkage

Record linkage techniques have been used to enable researchers to identify and merge data regarding a single individual stored in different databases. Within this thesis record linkage followed the methods described by Bohensky *et al (452)* to find records within the datasets that were linked to the each individual patient across different data sources that were available from Fife and Tayside. Linkage was conducted via CHI seeding which has handled by the HIC data officer and then released to the principal investigator with corresponding unique PROCHI ID (which is a simulated CHI number used by HIC) for each patient in accordance with the data access protocols of anonymisation.

The data linkage procedure used to identify explanatory variables is depicted in the flow chart below.

Flowchart of the data linkage process



4.8. Chapter summary

This chapter explained the methods used to link the data to make up one composite dataset. The final variables and how the matching of variables was achieved were demonstrated. The data cleaning and linkage procedures were laid out. Assignment of key variable information such as alcohol and smoking status as well as comorbidity status were also explained. As the data was collected in different regions of Scotland, there is a high likelihood of a lack of consistent measurement of key variables e.g. TNM was recorded as the full values in Tayside and yet in Fife, all three values were recorded in individual columns. It was necessary to begin with this and then highlight proposed methods to analyse data such as survival analysis and any statistical methods for dealing with missing data. The next chapter will give an overview of the survival analysis proposed to deal with the linked health data for the Fife and Tayside cohorts of HNC patients.

Chapter 5

5.1. Cohort Analysis Methods

5.1.1. Chapter Outline

This chapter outlines the methods for the statistical analysis of the linked retrospective cohort data for Fife and Tayside. Description, definition of the cohort, assignment and calculation of variables such as HNC type and ECI measured comorbidity will be given. The key variables of comorbidity and SES had to be adequately described for each patient as they are ultimately useful for assessing their prognostic impact. The primary and secondary outcome measures will be explained as well as how missing data will be accounted for using statistical methods. Analysis of survival will be conducted using the Kaplan-Meier method and the log-rank test, with key explanatory variables analysed using multivariate survival analysis using the Cox proportional hazards regression model. The hazard ratios (HR) with their 95% confidence intervals (CI) will be reported to assess the corresponding survival estimates dependent on explanatory variables.

5.2. Identifying the cohort

In order to have access to patient data to conduct the analysis investigating the influence of both comorbidity and SES, approvals to conduct the research had to be obtained. These approvals were sought from the respective NHS Fife's and NHS Tayside's Caldicott Guardians as well as the custodian for the Fife data JP, the HNC Specialist Nurse. Ethical approval was not required for this project as the patient data was anonymised meaning that there was no identifiable information within the dataset. The data was made available through the Safe Haven which is a secure access portal administered by the HIC team at University of Dundee. In order to obtain Safe haven access, the PI had to submit a protocol and data analysis plan to the HIC.

The final patient cohort was derived from 2 sources; for Fife a database containing all known diagnoses of HNC was being prospectively compiled by the HNC Specialist Nurse. The second data source for Tayside patients was based on a retrospective case note review conducted by a research assistant. The source of these patient files were the following departments, Oral and Maxillofacial, Ear Nose and Throat, as well as Oncology at Ninewells Hospital in Dundee. To ascertain that all the patients in both the Fife and Tayside cohorts had a diagnosis of HNC, diagnostic codes relating to HNC from the International Statistical Classification of Diseases and Related Health Problems 10th edition (ICD-10) (7) were cross matched against the SMR06 Cancer Registry codes for both cohorts. We used a tool provided by MacMillan (5) to assign ICD-10 codes to the different HNC sub-sites. The head and neck three character ICD-10 site codes categorise the HNC to its point of origin within a specific structure such as the larynx or tonsils. These codes can be broken down into the specific location within the structure such as in malignant neoplasm of the gum. The corresponding code of C03 is subdivided into upper gum C03.0. The lower gum has an ICD-10 code of C03.1. There is also a subcategory .9 which is used when the sub site is not specified. From using coding methods as broken down into the steps similar to the preceding example, there were no major issues assigning the codes for the HNCs. Even though there has been some debate in the case of oropharyngeal cancer particularly for the area behind the wisdom teeth (called the retromolar trigone) which can be included as a part of the oral cavity. As it is often considered part of the oropharynx, it was included as part of the oropharyngeal subsite. The oropharynx is the part of the throat just behind the mouth. It begins where the cavity stops. It includes the base of the tongue (the back third of the tongue), the soft palate (the back part of the roof of the mouth), the tonsils, and the side and back wall of the throat. We were able to assign ICD-10 codes by specifying the exact structures of the oropharynx.

Figure 15 ICD-10 codes for HNC

Site	ICD-10
Lips	C00
Tongue	C01–C02
Gums	C03
Mouth floor	C04
Major salivary glands	C07–C08
Palate	C05
Other parts of the mouth	C06.0–C06.2
Tonsils	C09
Oropharynx	C10
Nasopharynx	C11
Piriform sinus	C12
Hypopharynx	C13
Malignant neoplasia of other sites; ill-defined and unspecified sites of lips, oral cavity, and pharynx	C14; C06.8; C06.9

Adapted from Boing *et al* (453)

The SMR01 data was used to highlight any hospital discharges for concomitant disease other than the index disease, HNC. The diagnosis code was matched to key comorbidity conditions listed in the two indices of interest, CCI and ECI.

5.2.1. Variables under study

Date of diagnosis was taken from that specified in the datasets provided for both geographic regions. If this was unavailable, the date identified in the cancer registry was taken as the diagnosis date. Notably the earliest diagnosis date was used if there were any disparities identified. The date of death was taken from the GRO deaths records data and used in place of the one already recorded within the initial dataset information due to the higher reliability of the GRO data.

5.2.2. Primary outcome measure

All cause mortality was considered as the primary outcome of interest as it accounts for variations in the data available for all patients in the cohort. Date of death was obtained from GRO death records as this government source is a more robust source of information compared to data collected by an individual which are prone to non-systematic bias.

5.2.3. Secondary outcome measures

Cause specific survival was chosen as the a net survival measure representing cancer survival in the absence of other causes of death. It was deemed the most reliable method to estimate the probability of surviving HNC within the cohort under study. Patients with cause of death according to GRO data listed as HNC death were flagged while other cancers were censored. Disease free survival was measured as the amount of time that a person with HNC survived without known recurrence of the cancer. The duration before recurrence was calculated from initial diagnosis date to the date when recurrence of HNC was recorded.

5.2.4. Characteristics of the cohort

Age at diagnosis for each patient was calculated using date of birth from diagnosis date. This is the age used throughout the analysis. There were a small number of patients who did not have a date of birth and these were excluded from the analysis. Patients were allocated into age bands ranging from 0-19, 20-39, 40-59, 60-79, and 80-99 years. Comorbidity is an important prognostic factor with evidence from the principal researcher's review found that the more severe the comorbidity level, the higher the likelihood of premature death in patients with HNC. (163, 299, 330, 338, 343) In order to measure comorbidity within the cohort, the literature was reviewed and it was decided to employ the ECI and CCI comorbidity Indices.

de Groot *et al* pointed out that survival studies can also be complicated by comorbidity as it can either act as a confounder, threatening the internal validity, or as an effect modifier, threatening the internal and external validity of the study. (454) For that reason it was decided to employ an efficient method to measure comorbidity due to four important reasons, namely to be able to correct for confounding, and improve the internal validity of the study, to identify effect modification, while also facilitating the applicability of comorbidity as a predictor of outcome, and finally, a comprehensive comorbidity measure, including many co-occurring comorbid conditions in one valid variable, was required to enhance statistical efficiency. Despite numerous comorbidity measures in existence for use in HNC, there is no identified "gold standard" index available for measuring comorbidity. Due to this, the principal researcher decided to use two indices for comparison purposes the CCI and the ECI which have been shown to be both valid and reliable in comorbidity measurement in HNC. (333) Initially the intention had been to use the ACE-27 index. The ACE-27 classifies comorbid conditions and ailments separately as no comorbidity, mild, moderate, and severe according to the degree of organ decompensation and prognostic impact. (148) These grades are then used to assign patients to their overall comorbidity, the overall ACE-27 ranking being equated to the highest ranked ailment. Patients with more than two moderate ailments in different organ systems are graded overall as severe. It is a modification of the Kaplan–Feinstein index (KFI) (455) and has been validated for head and neck cancer,1 although its use has not been widely reported in patients with head and neck cancer in the United Kingdom.(299, 456) Despite the obvious advantages of using the ACE-27 index, this had to be shelved as this index requires access to patient records which was not possible at this stage of the research project. Comparison was carried out using both statistical tests to test which comorbidity measure was the best predictor of mortality.

The Charlson Index (99) has been used extensively and has been identified as suitable for use in HNC studies. (89, 163, 337, 457) The 19 diseases included in the index have been selected and weighted on the basis of the strength of their association with mortality. A person's Charlson

index is the sum of these weights. The index was first validated in a cohort of patients with breast cancer, with the weights derived from regression coefficients predicting survival.

SES; in particular, income (108, 362)and education as the main domains within SIMD, were shown in an earlier systematic review by the principal researcher to affect survival prospects. (167, 309, 355, 359) The marker for deprivation within this cohort was the SIMD specifically the income and education domains were included in the analysis.

Tumour characteristics- TNM classification of cancers of the head and neck) are provided below, along with anatomic staging. This translated to tumour size, presence of regional node metastasis and any distant metastasis. The categories for each HNC type are listed in below.

Table 13 Types of HNC

HNC Types	
1.	Hypopharyngeal cancer
2.	Laryngeal cancer
3.	Mouth (oral cavity) cancer
4.	Nasopharyngeal cancer
5.	Oropharyngeal cancer
6.	Paranasal sinus cancer
7.	Salivary gland cancer

Source: Macmillan (5)

5.2.5. Identifying cause of death

In Scotland the death certificate lists the cause of death as follows:

An immediate cause of death is given, and then a process of retracing the disease or condition that started the process is commenced. It identifies:

- the disease or condition that led directly to the death;
- any antecedent or intermediate causes of that disease or condition (i.e. which occurred earlier in the chain of events that led to the death); and, eventually, goes back to -

- the underlying cause of death which is defined in the ICD-10 (7)as: "(a) the disease or injury which initiated the chain of morbid events leading directly to death or (b) the circumstances of the accident or violence which produced the fatal injury". (458)

In order to identify the immediate cause of death and any underlying causes, the ICD-10 codes will be retrieved and matched to the immediate cause of death and the specific underlying conditions.

5.3.1. Statistical methods - Defining outcome measures

Patient follow-up was until death or 31.12.2013 the date of the last records available for study. All other records were considered alive for the analysis unless their death was already recorded in the GRO death dataset. This meant that all events up to and including that date were considered for the analysis. For the purpose of this thesis it is important to highlight the primary and secondary outcome measures. The primary outcome of interest is death from all causes. All cause mortality is a robust method for measuring outcomes in cancer. To give the findings better generalisability, it was also determined that HNC specific survival would enhance study outcomes. Initially the PI had intended to measure recurrence free survival as a secondary outcome but due to the low incidence of recurrence within the cohort, this outcome will not be explored. The methods used to account for this are explained below.

5.4. Multiple imputation methods

Missing data poses serious challenges that have to be accounted for when dealing with multivariate data such as in this project. The missing values that are referred to in this project are the values that should have been present in the Fife and Tayside datasets but were either missing or absent. These data could have been missing for a variety of reasons such as:

a) the person doing data entry was not trained and there was a possibility that data collection was not done systematically
b) There may have been errors in data entry which led to missing values
c) The Fife dataset was almost double that of Tayside which may have led to more errors due to data management shortcomings
d) Some of the data was based on self response such as smoking and alcohol status allocation therefore some patients may have been unwilling to provide a response to questions
e) The Fife data were collected prospectively; therefore it is possible that some patients died before all the relevant information could be collected.

In order to estimate the missing values multiple imputation was used, which refers to the process of replacing the missing values with plausible answers. (459) In order to identify which of the key variables had missing values, frequency distributions were obtained for these variables namely HNC type age group, smoking and alcohol status, stage of disease, Scottish SIMD quintile, SIMD income and education domains as well as ECI and CCI classification.

A missing values analysis showed that the information was missing at random as there was no evidence of a pattern of missingness in the data. (460). As a result the statistical approach taken was chained imputation as no assumptions were made about missingness or patterns of distribution of the variables. Chained imputation as defined by Woodward (459) is known as regression switching or sequential multiple imputations. It is an iterative process that is dependent on the type of data and uses a sequence of univariate imputations, e.g. binary variable imputations use logistic regression.

The modeling procedures available in SPSS version 22 which was used to conduct the analysis resulted in 199 cases being excluded from the analysis. This loss of cases meant that out of the total cohort of 1344 patients, 14.8% was excluded due to missing data for any variable. In essence

only 1145 could potentially be included in the analysis. Had our sample been large, we may have been able to allow for these 199 cases to be excluded from the analysis but this was deemed unsuitable unless a missing value could ascertain the pattern of missingness of the data which might allow exclusion of those cases.

The missing values analysis allowed us to determine whether the complete case analysis (list wise deletion) performed using SPSS was sufficient and relevant in this instance. We adopted a three stage approach as follows:

- We sought to obtain a full description of the distribution the number of cases missing per variable
- We sought to clarify the pattern of the missingness of the data specifically we considered the probability of missingness, i.e. where there certain cases in the cohort that were more likely to have missing values?
- This information allowed us to make decisions on which approach we would from the available options of dropping those cases from the analysis, or using substitution methods i.e. single or multiple imputations to create values where these were missing.

In order to make sound judgments on the data we also had to evaluate whether the patterns of missingness were

1. Missing completely at random (MCAR) – the missing value neither depends on an observed value or one that has not been observed within the dataset. An example that would apply to this dataset is the disease staging was not recorded as the patient died before such information could be ascertained
2. Missing at Random (MAR) Missing value (y) depends on x, but not y

Example: Respondents in service occupations less likely to report income

Missing not at Random (NMAR) The probability of a missing value depends on the variable that is missing

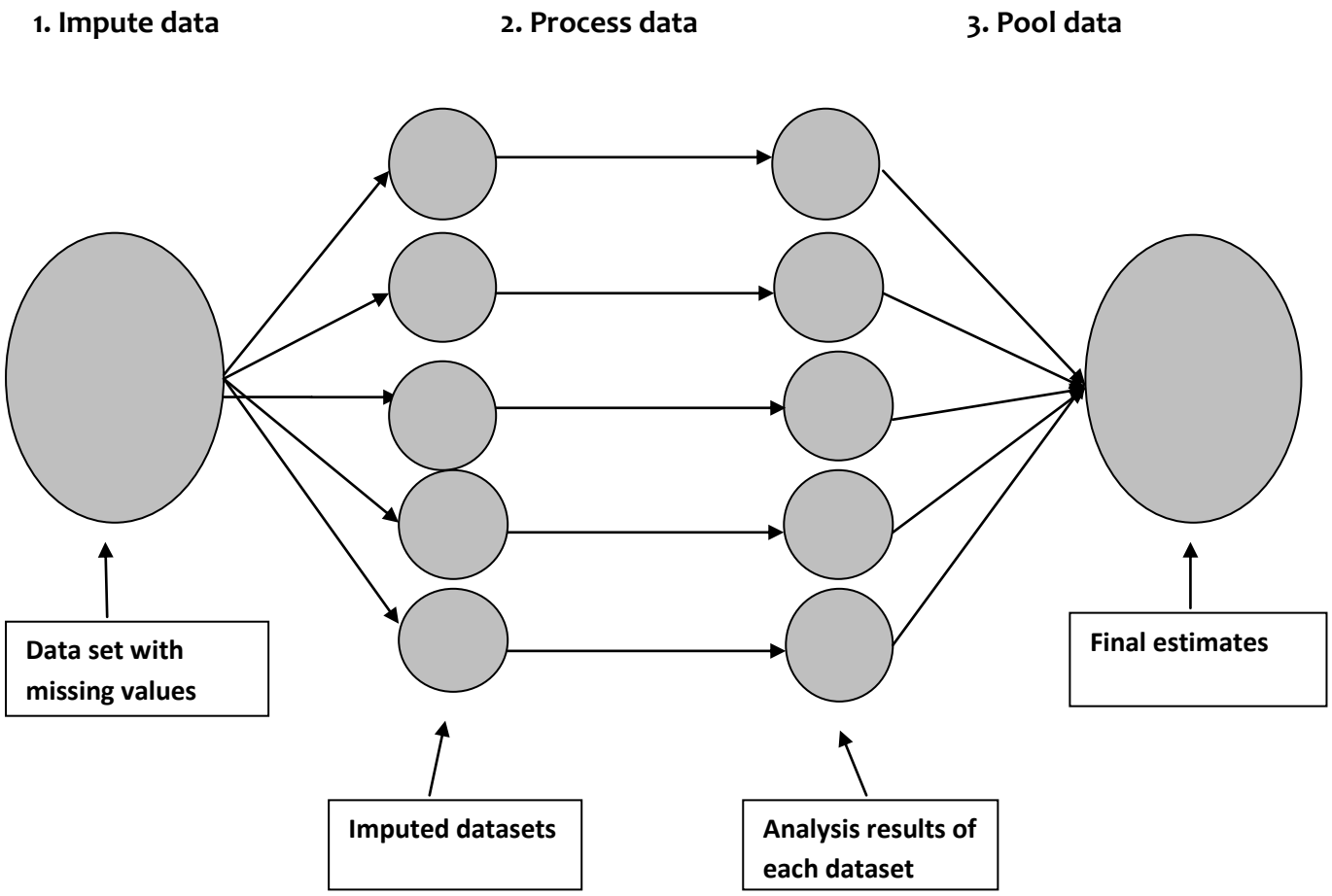
Example: Respondents with high income are less likely to report income

As the patient sample was relatively small, a substitution method had to be used to allow for the retention of enough cases to have sufficient power with our study to detect any prognostic influence effects from the factors under study. The results of this analysis are presented in the results section, however as a result of these findings we had to use the multiple imputation method to substitute

5.4.1. Rationale for using multiple imputations

The missing data was especially apparent in the Fife cohort and as this contributed the largest number of patients. Multiple imputation models were created in order to estimate the values for the missing records. Using this method made it possible to account for missing data which meant that list-wise deletion of the large number of cases that had missing values was avoided which saved time. The major advantage for using multiple imputation methods is that once all missing values had been imputed, the data set was ready for analysis using standard techniques for complete data.

5.4.2. Multiple imputation process



5.5. Statistical methods for the survival analysis

In order to ascertain time to the event of interest, death, survival analysis was deemed to be the preferred and logical method to conduct the analysis. In general the amount of data generated from merging the Fife and Tayside patient files, meant that a large number of variables were in the dataset. The next step was to provide the descriptive analysis of the population characteristics and any explanatory variables. This included an overview of the age and gender distribution of the cohort. The incidence of comorbidity and SES groupings within the cohort were also described.

The analysis commenced with Kaplan Meier curves to examine the number of patients surviving without experiencing the event of interest, death. This was analysed using age, gender, HNC

subtype, comorbidity, and SES. As tumour staging information was complete for only the Tayside portion of the cohort, the survival plots presented only apply to that population. The Kaplan Meier method was also selected as it allowed for comparison of survival between groups. The analysis the proceeded to Cox proportional hazards regression which allowed for the assessment of the individual effect of the same explanatory variables used in the Kaplan Meier survival analysis.

The fit of the Cox Proportional hazards model to the study data were tested using two complementary methods:

1. Area under curve or Receiver operating statistic (C-statistic) (461) is a method that has been used to evaluate the overall performance of the risk scoring system. It is an established measure of model discrimination for binary outcomes and works well when applied to survival data. Values for the C statistic range from 0.5 to 1.0. A value of 0.5 is indicative that the model is no better than chance at making a prediction of the model fit. A C-statistic that is higher than 0.7 is considered reasonable while 0.8 is considered strong. A value of 1.0 indicates that the model perfectly fits the data.
2. Akaike information criterion (AIC) (462) is a framework that allows simultaneous estimation and selection. This statistic illustrates how well the Cox model conforms to the observed data in the cohort. The following criteria are used to determine the applicability of levels of the AIC.

Table 14 AIC criteria

AIC	Level of empirical support for AIC
0-2	Substantial
4-7	Considerably less
>10	Essentially less

Source: Burnham and Anderson (463)

After reviewing the individual effect of each predictor variable, the PI was able to assess the combined effect of these variables in a single Cox regression to address the hypothesis that low SES and severe comorbidity are linked to poor survival. The final Cox model calculated the hazard or probability of death using the following equation: $H(t) = H_0(t) \times \exp(b_1X_1 + b_2X_2 = b_3X_3 + \ldots.. b_kX_k)$. All the statistical analyses were conducted in SPSS version 22.

5.6. Chapter Summary

This chapter gave a synopsis of the planned statistical analysis highlighting both the descriptive statistics as well as the survival analysis methods. It also explains how the findings of the systematic review which were used in the analysis fed into the selection of predictors was described. In addition the methods for dealing with missing data were explained by the use of missing values analysis and multiple imputations. The results of the statistical analysis are presented in the next chapter.

6.1. Survival Analysis Results

6.1.1. Chapter Outline

This chapter will depict the findings from the analysis that was proposed in the preceding chapter. A description of the cohort attributes will be explained in relation to the outcomes of interest in this study. Survival analysis methods will be used to assess the prognostic contribution of both comorbidity, (defined using the CCI and ECI) and SES (using the Scottish SIMD quintiles and the income and education domains of the SIMD) will be presented in the order of the research questions and the hypothesis underpinning this study. The analysis was done initially by region to test the hypothesis and evaluate whether either region had data that corresponded or disputed the results of the systematic review. This was done using survival distributions and cross tabulation to assess whether there were associations between stage at presentation with SES and if comorbidity and SES were prognostic factor for survival. Due to missing data multiple imputations were used to account for missing data. The results of the two regions were compared and the final analyses looked at a combined cohort as the bigger numbers gave the study greater power.

6.1.2. Introduction

The cohort was initially made up of 1384 patients but this was reduced to 1344 due to removal of duplicate patient records and also some ineligible cancers (thyroid n=9, oesophagus n=2) that occur in the head and neck region but do not fall under the HNC definition used in this thesis. Out of the cohort of 1344 patients, 524 (39%) deaths had occurred by 31st December 2013.

6.1.3. Cohort definition

The description of the entire cohort is displayed in Table 15 and the analysis by each individual sub-cohort and followed by the combined cohort results.

Table 15 Full cohort characteristics

Variable	N	%	Variable	n	%
	Sex			**Comorbidity**	
Female	429	31.9	**Charlson comorbidity index**		
Male	913	67.9	**None**	132	9.8
Missing	2	0.1	**Mild**	28	2.1
Age groups			**Moderate**	244	18.1
<40 years	20	1.5	**Severe**	745	55.4
41-50 years	67	5.0	**Missing**	195	14.5
51-60 years	231	17.2	**Elixhauser comorbidity index**		
61-70 years	382	28.4	**None**	856	63.7
71+ years	517	38.5	**Mild**	148	11.0
Types of HNC			**Moderate**	127	9.4
Mouth	260	29.7	**Severe**	19	1.4
Laryngeal	233	29.6	**Missing**	194	14.4
Oropharyngeal	112	12.8	**Smoking status**		
Hypopharyngeal	14	1.6	**None smoker**	214	15.9
Paranasal sinus	20	2.3	**Ex smoker**	247	18.4
Nasopharyngeal	15	1.7	**Moderate**	141	10.5
Salivary gland	37	4.2	**Heavy smoker**	317	25.6
Missing	185	21.1	**Missing**	425	31.6
Stage			**Income quintiles**		
Stage 0	54	4.0	**Most deprived**	154	11.4
Stage 1	202	15.0	**Quintile 2**	112	12.8
Stage 2	143	10.6	**Quintile 3**	135	15.4
Stage 3	151	11.2	**Quintile 4**	202	23.1
Stage 4	392	29.2	**Least deprived**	210	24.0
Missing	402	29.9	**Missing**	132	15.1
Scottish SIMD quintiles			**Education quintiles**		
Most deprived	278	20.7	**Most deprived**	158	11.8
Quintile 2	261	19.4	**Quintile 2**	206	15.3
Quintile 3	228	17.0	**Quintile 3**	198	14.7
Quintile 4	211	15.7	**Quintile 4**	283	21.1
Least deprived	153	11.4	**Least deprived**	295	21.9
Missing	213	15.8	**Missing**	202	15.0
	Alcohol status				
None drinker	126	9.4			
Moderate drinker	253	18.8			
Harmful drinker	130	9.7			
Hazardous drinker	248	18.4			
Missing	587	43.7			

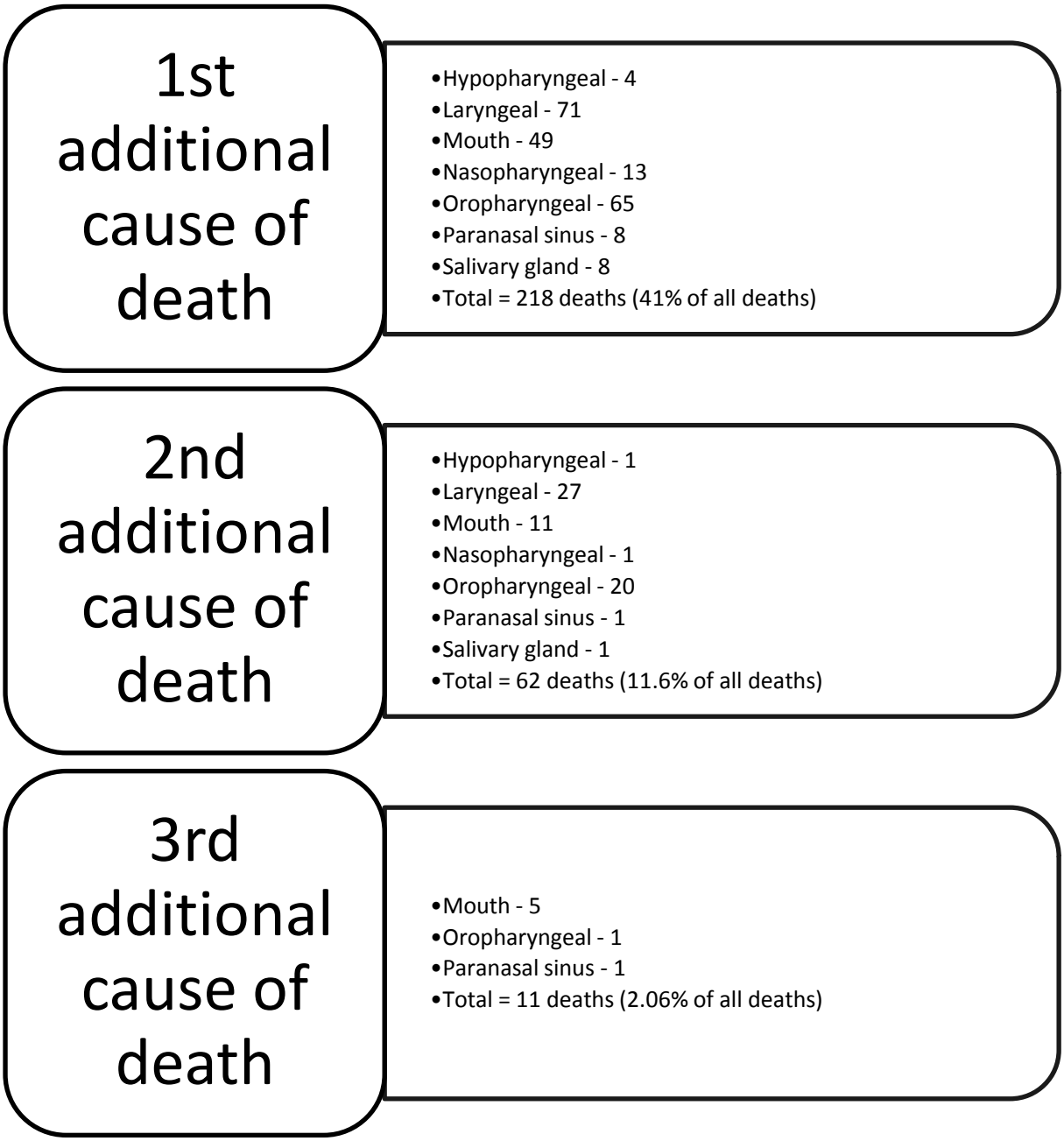
The causes of the deaths that occurred within the cohort are tabulated below (Table 16).

Table 16 Main cause of death in the cohort

Main cause of death	n	%
HNC	225	42.9
Other tumours	123	23.5
Circulatory system disorders	46	8.8
Respiratory disorder	35	6.7
Immune system disorders	30	5.7
Central nervous system disorders	27	5.1
Alcoholism	10	1.9
Digestive disorders	8	1.5
Missing cause of death	6	1.1
Death from complications	4	0.8
Accidental death	2	0.4
Musco-skeletal disorders	2	0.4
Total deaths	524	100.0

As per Scottish death certification, we found that HNCs were the main cause of death accounting for 42.2% of deaths within the cohort, leaving 52.7% of the cohort alive after the end of 2013. For additional causes of death, the distribution of HNC types and their contribution to death is shown in figure 16.

Figure 16 HNC contributions to additional causes of death



In order to describe the cohort further, a table on the distribution of the comorbidities by the specific comorbidity measure is presented.

Table 17 Distribution of patients by comorbidity measure

Charlson comorbidity index (CCI)	n	%	Elixhauser comorbidity index (ECI)	n	%
AIDS/HIV	0	0	Alcohol abuse	75	5.6
Cerebrovascular disease	0	0	Blood loss anaemia	0	0
CHF	8	0.6	Cardiac arrhythmia	0	0
Connective tissue disease	0	0	CHF	8	0.6
CPD	101	7.5	Coagulopathy	19	1.4
Dementia	12	0.9	CPD	101	7.5
Diabetes mellitus	147	10.9	Complicated diabetes	2	0.1
Diabetes with chronic complications	0	0	Complicated hypertension	0	0
Hemiplegia	9	0.7	Deficiency anaemia	0	0
Leukaemia	11	0.8	Depression	3	0.2
Lymphoma	21	1.6	Drug abuse	4	0.3
Metastatic tumour	0	0	Fluid & electrolyte disorders	0	0
Mild liver disease	51	3.8	Hypothyroidism	0	0
Moderate to severe liver disease	0	0	Liver disease	58	4.3
PVD	86	6.4	Lymphoma	21	1.6
Renal disease	0	0	Metastatic cancer	0	0
Solid tumour	0	0	Obesity	20	1.5
Ulcer disease	0	0	Other neurological disorders	0	0
			Paralysis	8	0.6
			PVD	86	6.4
			Psychoses	3	0.2
			Pulmonary circulation disorders	0	0
			Renal failure	27	2.0
			Rheumatoid arthritis	19	1.4
			Solid tumour without metastasis	0	0
			Ulcer disease	0	0
			Uncomplicated hypertension	0	0
			Valvular disease	0	0
			Weight loss	47	3.5
			AIDS/HIV	0	0

A total of 587 (43.7%) patients had CCI measured conditions. Diabetes mellitus 147 (10.9%), myocardial infarction 141 (10.5%), chronic obstructive pulmonary disease 101 (7.5%), peripheral vascular disease 86 (6.4%) and mild liver disease 51 (3.8%) were the most common comorbidities. The less common conditions included lymphoma 21 (1.6%) hemiplegia (1.0%), dementia (0.9%), leukaemia 11 (0.8%) and congestive heart failure (0.6%).

For ECI there were a total of 285 (21%) comorbidities in the cohort. These were made up of alcohol abuse (5.6%), liver disease 58 (4.3%), weight loss 47 (3.5%), renal failure 27(2%), obesity 20

(1.5%), coagulopathy 19 (1.4%), rheumatoid arthritis 19 (1.4%), paralysis 8 (0.6%), drug abuse 4 (0.3%), depression 3 (0.2%), psychoses 3 (0.2%), and diabetes with chronic complications 2 (0.1%).

The distribution of comorbidity classification for these patients based on the comorbidity index is shown in Table 18 and 19. The no comorbidity and the mild comorbidity groups in the CCI were combined into one group due to very few numbers in both groups as this would have complicated the results of any subsequent analysis particularly the proportional hazards regressions.

Table 18 CCI distribution by comorbidity classification

Explanatory variable	Frequency	Percent
None/Mild comorbidity	160	11.9
Moderate comorbidity	244	18.2
Severe comorbidity	745	55.4
Total	1149	85.5
System missing	195	14.5
Total	1344	100.0

Table 19 ECI distribution by comorbidity classification

Explanatory variable	Frequency	Percent
No comorbidity	856	63.7
Mild comorbidity	148	11.0
Moderate comorbidity	127	9.4
Severe comorbidity	19	1.4
Total	1150	85.6
System missing	194	14.4
Total	1344	100.0

6.2.1. Fife cohort

The Fife cohort had 844 patients who were included in the analysis, including 593 (67.7%) males and 281 females (32.1%), and the largest group of patients were aged over 71 years (42.2%). Patients aged ≤50 years made up only 5.2% of the cohort. 42.2% of the patients had a smoking status of heavy/ex/moderate, and 38.3% of patients represented the harmful and hazardous drinkers combined. The types of carcinoma included 29.7% mouth and 29.6% laryngeal cancer.

Most of the patients were in stage IV (24.2%) and 11.8% patients were in stage I. Over half of the patients had a CCI score of moderate or severe comorbidity with both categories making up 28.3% and 35% respectively. The ECI score of no comorbidity had 62.1% share of the cohort while only 96 patients had moderate comorbidity and 12 patients had an ECI score of severe comorbidity.

After conducting an analysis using cross tabulation to identify any patterns within the data, a trend for increasing severity of comorbidity was noted for age, see the cross tabulation of CCI and age.

Table 20 Cross tabulation of Age and CCI

Age	**CCI**				**Total**
	None	**Mild**	**Moderate**	**Severe**	
<40 years	10	0	0	0	10
41-50 years	12	18	4	2	36
51-60 years	22	28	50	14	114
61-70 years	29	6	137	49	221
71+ years	59	11	57	242	369
Total	132	63	248	307	750

An association of comorbidity status having an increasing severity in relation to worsening disease stage was also confirmed. Using cross tabulation we found that more patients from lower SES backgrounds presented with advanced disease, see Table 21.

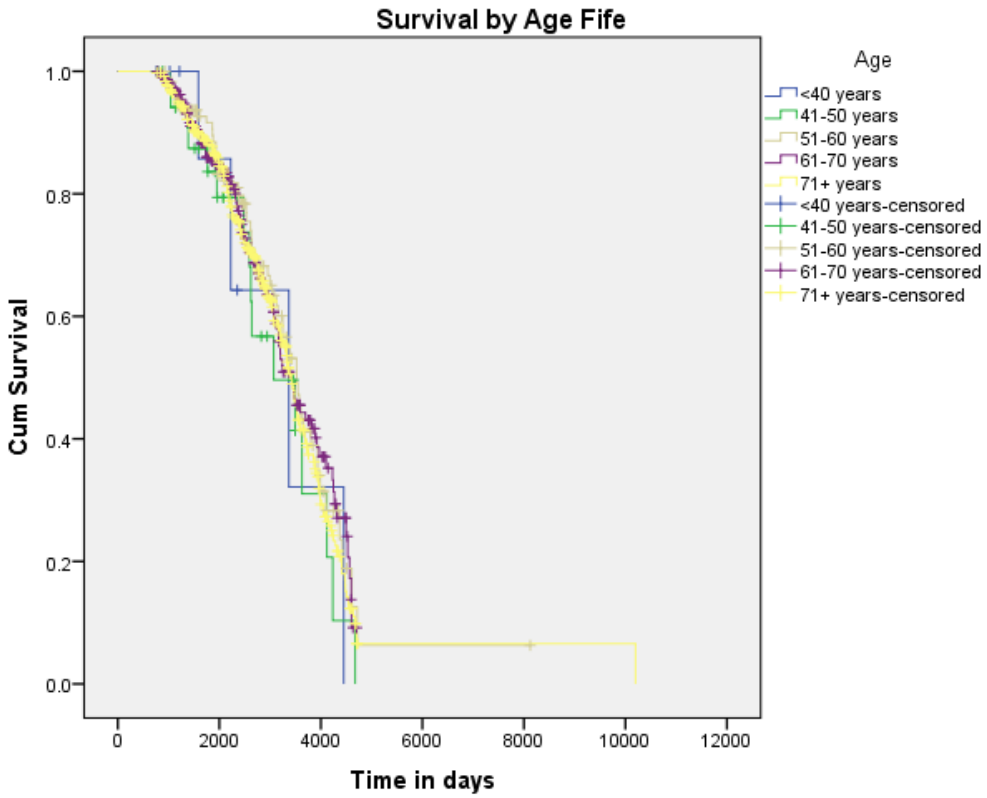
Table 21 Cross tabulation of Disease stage by Income Quintile

Income Quintiles		**Stage**				**Total**
	Stage 0	**Stage I**	**Stage II**	**Stage III**	**Stage IV**	
Most deprived	2	12	9	4	17	44
2	2	12	12	12	21	59
3	1	14	8	15	43	81
4	0	34	20	20	54	128
Least deprived	4	22	19	28	65	138
Total	9	94	68	79	200	450

6.2.2. Results of Kaplan-Meier Analysis in Fife dataset

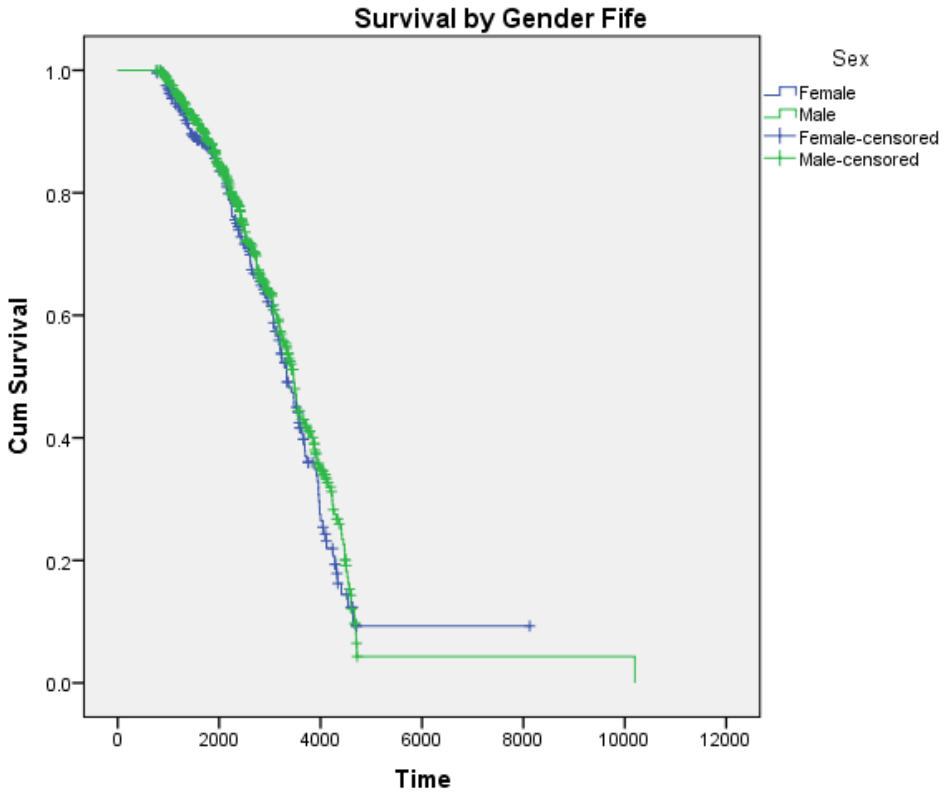
The survival distribution by age showed that the 71+ age group appeared to have a superior survival experience. The log rank test was used to test the null hypothesis using the χ^2 test and corresponding p value. Having inspected the cumulative survival plot (Figure 17) and reviewed the descriptive elements from our results using the Means and Medians for Survival Time output, we found that the age 71+ had better mean and median survival distributions with 3611.622 days compared to 3118.196 days for those aged 41-50 years. The log rank Chi-square (χ^2) test did not reach statistical significance with χ^2 of 1.702 and a p value of 0.790.

Figure 17 Fife survival distributions by age



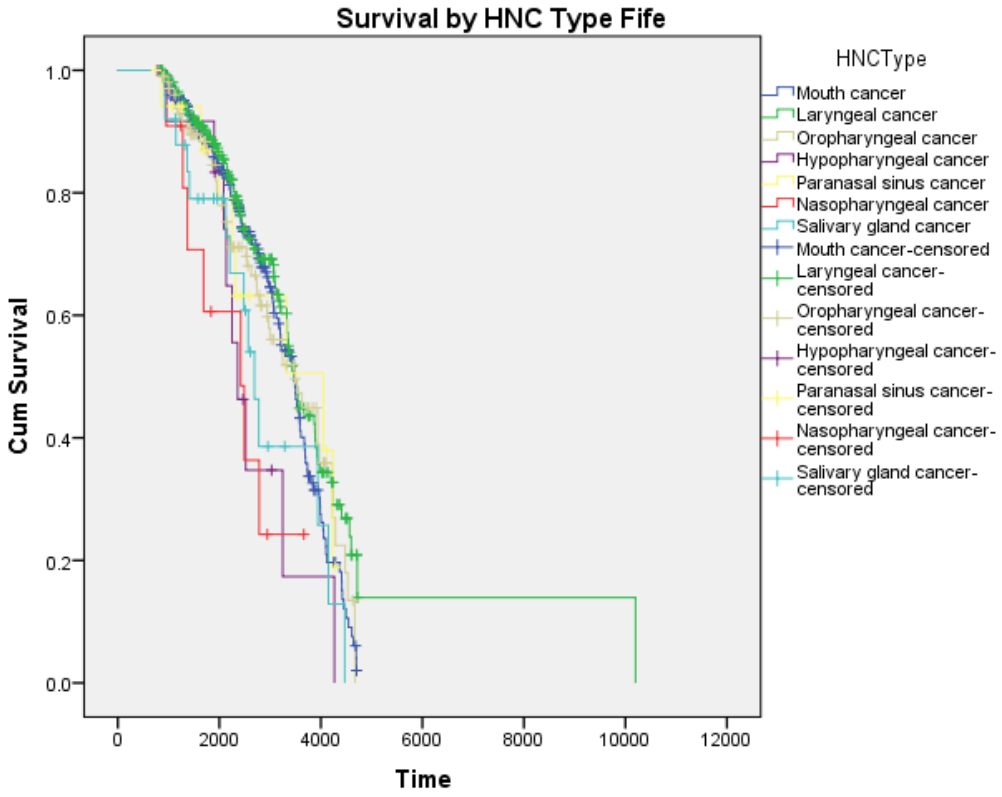
Survival distribution based on gender also did not reach statistical significance with a χ^2 statistic of 1.129 and p=0.288. The Kaplan-Meier output did however show that males appeared to have better survival outcomes with mean survival rates of 3560.259 days as rates for females were lower at 3519.176 days, (Figure 18).

Figure 18 Fife survival distributions by gender



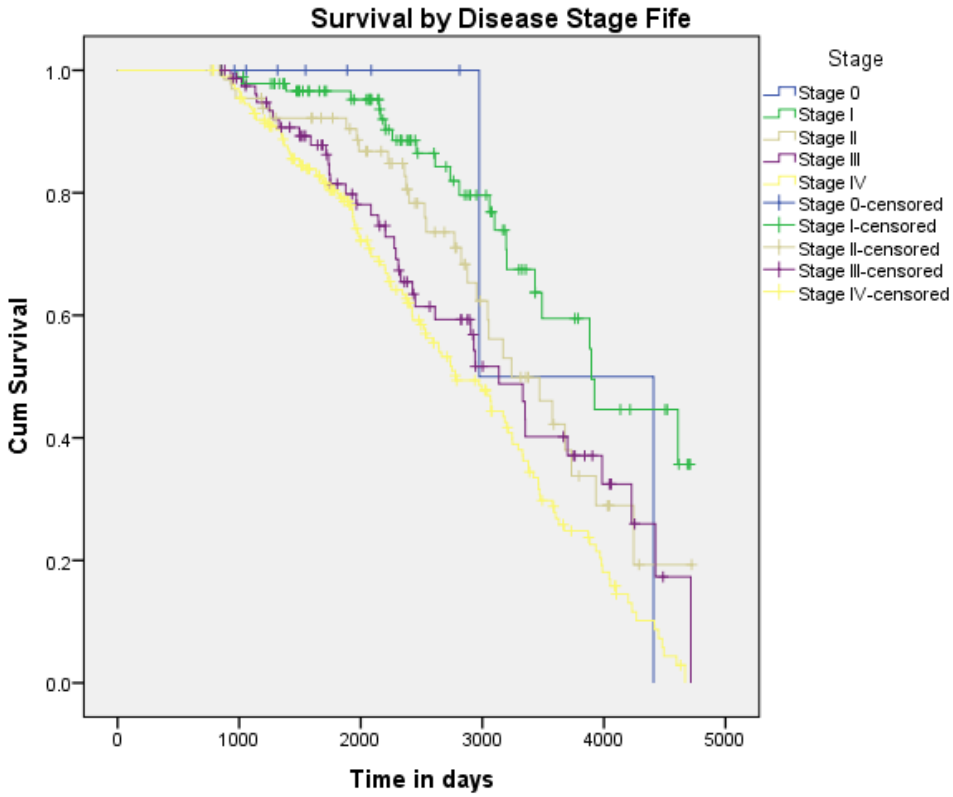
Next we assessed the survival distributions of the type of HNC within the patient group (Figure 19). We found that laryngeal cancer had the best overall mean and median survival times. In contrast patients who were diagnosed with cancers of the nasopharynx had the worst survival with mean survival time of 2346.202 days compared to 4165.917 days in laryngeal cancer. The log rank test did show a statistically significant difference in survival between the HNC Type groups with χ^2=17.510, p=0.008.

Figure 19 Survival distributions by HNC Type



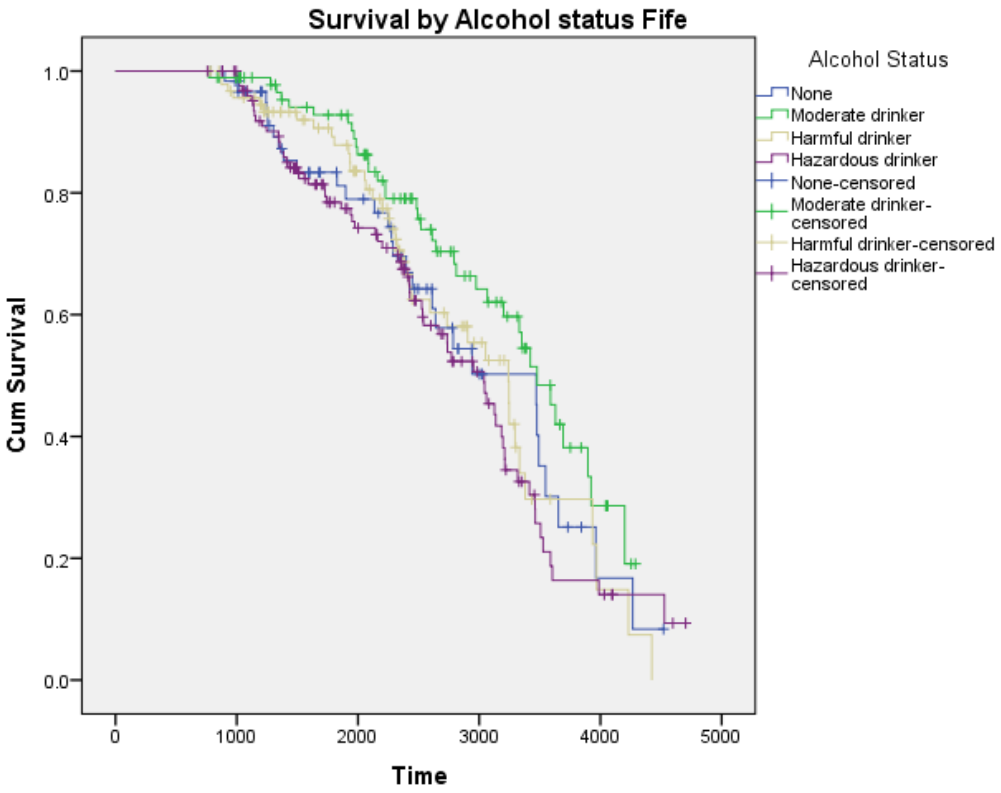
Disease stage was noted to have better survival distributions in patients with Stage 1 disease. Mean survival rates were compared and Stage 1 had the best survival at 3779.726 against the worst survival rate of 2835.671 in patients with Stage IV disease. This result was statistically significant with χ^2 test of 31.760 ($p<0.0001$). The Kaplan-Meier survival distribution is shown in the figure below.

Figure 20 Fife survival distributions by Disease stage



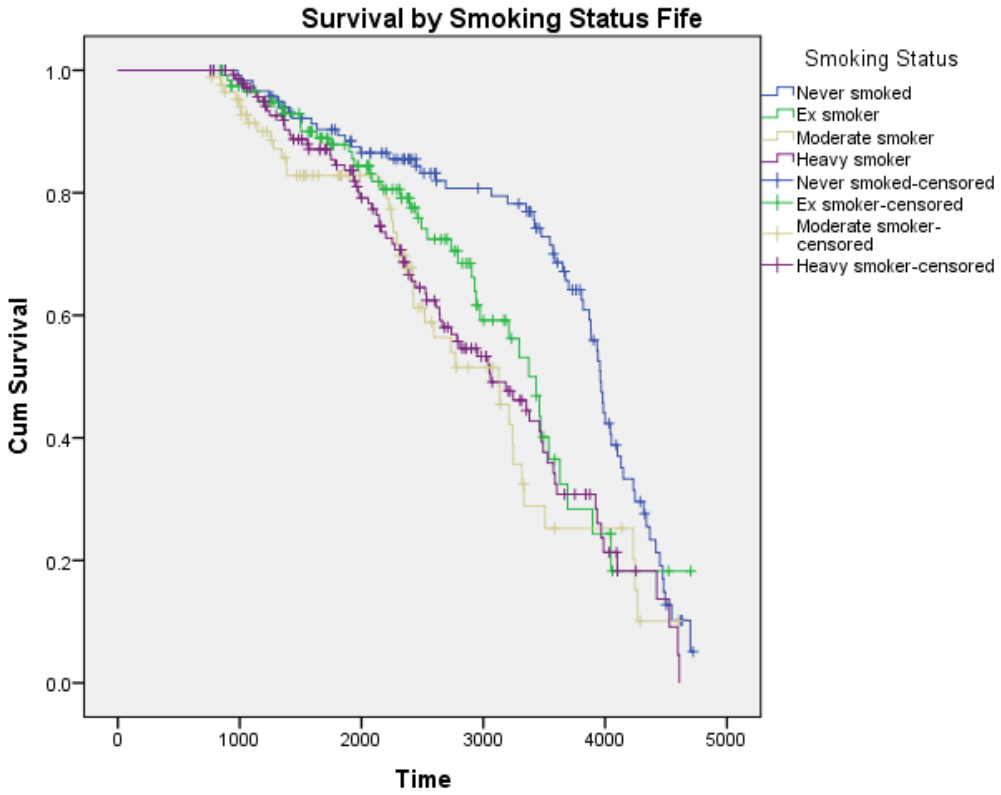
The log rank test that was run to determine if there were differences in the survival distribution for the different types of alcohol status: none drinkers, moderate, harmful and hazardous drinkers (Figure 21) found the survival distributions for the groups did not achieve the statistically significant difference with a $p<0.05$ with, $\chi^2= 7.306$, p 0.063. Hazardous drinkers had the worst mean and median survival times with mean of 2842.768 days in comparison to moderate drinkers who had mean survival of 3266.742 days.

Figure 21 Survival distributions by Alcohol Status



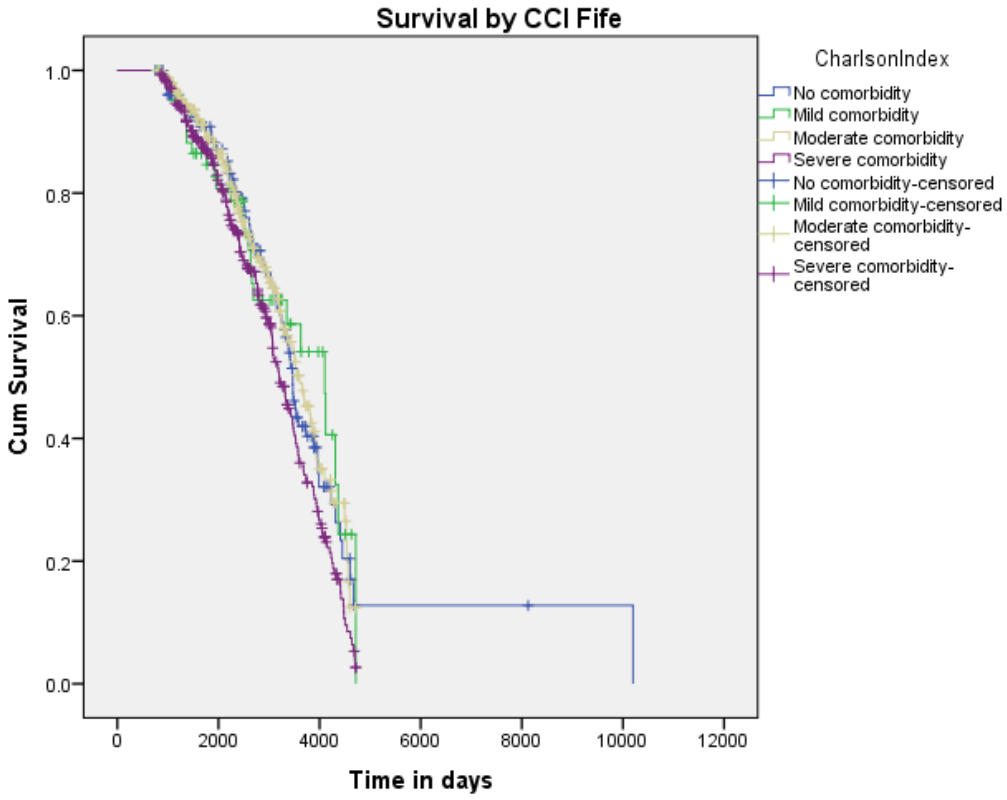
Cumulative survival for all smoking groups had evidence of statistical difference between groups with χ^2 of 17.866. These results were also shown to have reached statistical significance $p<0.0001$. Mean survival distributions for smoking status (Figure 22) did not follow a linear pattern with the worst outcomes for moderate smokers with mean survival of 2915.017 days compared to 3643.577 days for non-smokers.

Figure 22 Fife survival distributions by Smoking Status



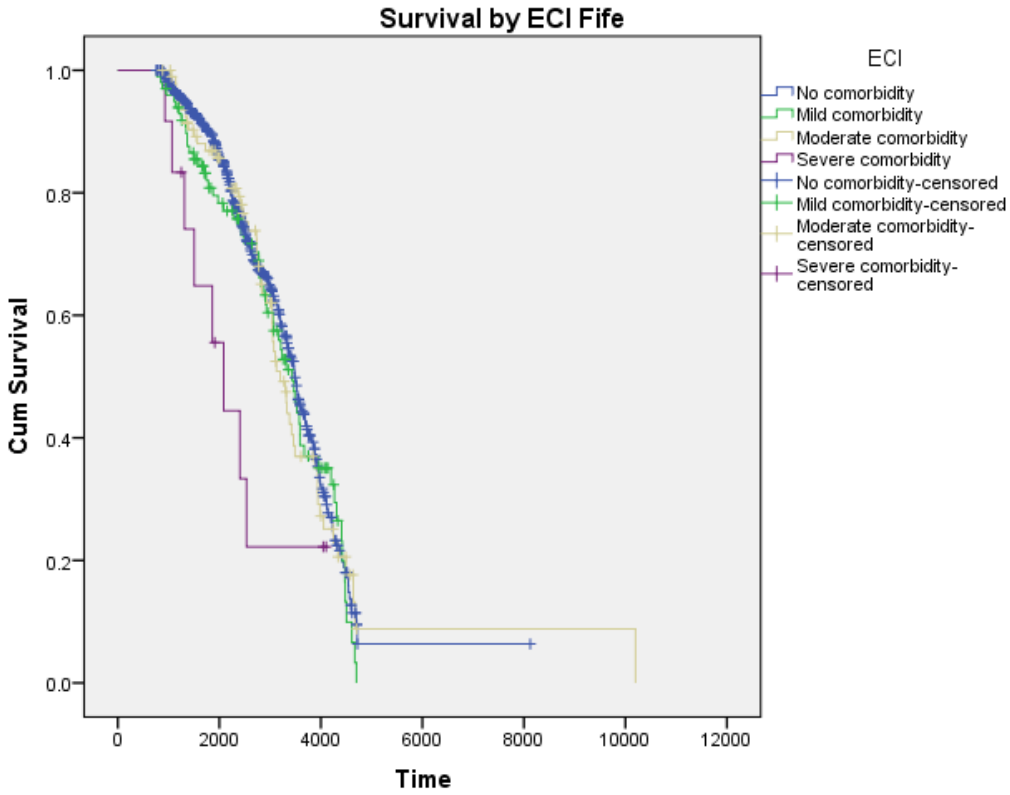
We began evaluating the two prognostic factors under study. Comorbidity measured by CCI appeared to demonstrate a divergence in cumulative survival which was shown to have statistical significance between the comorbidity groups. Severe comorbidity had the worst cumulative survival at 3132.877 days and the no comorbidity group had the best survival at 4077.387 days. The χ^2 statistic was 9.571 which was statistically significant with p=0.023.

Figure 23 Fife survival distributions by CCI



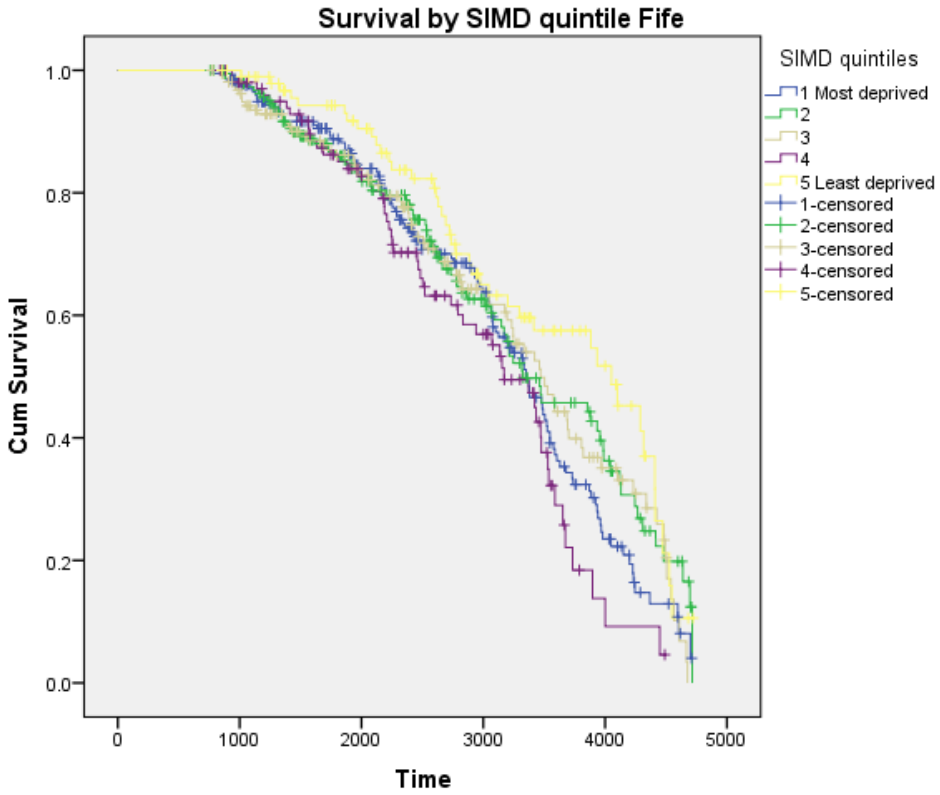
In the ECI model, (Figure 24) the group without comorbidity appeared to have a much higher cumulative survival compared to the groups with comorbidity. Comparison between the groups showed that the mean survival time for the no comorbidity group was 3719.195 days with a decline to 2292.500 days for those with severe comorbidity levels.

Figure 24 Survival distributions by ECI



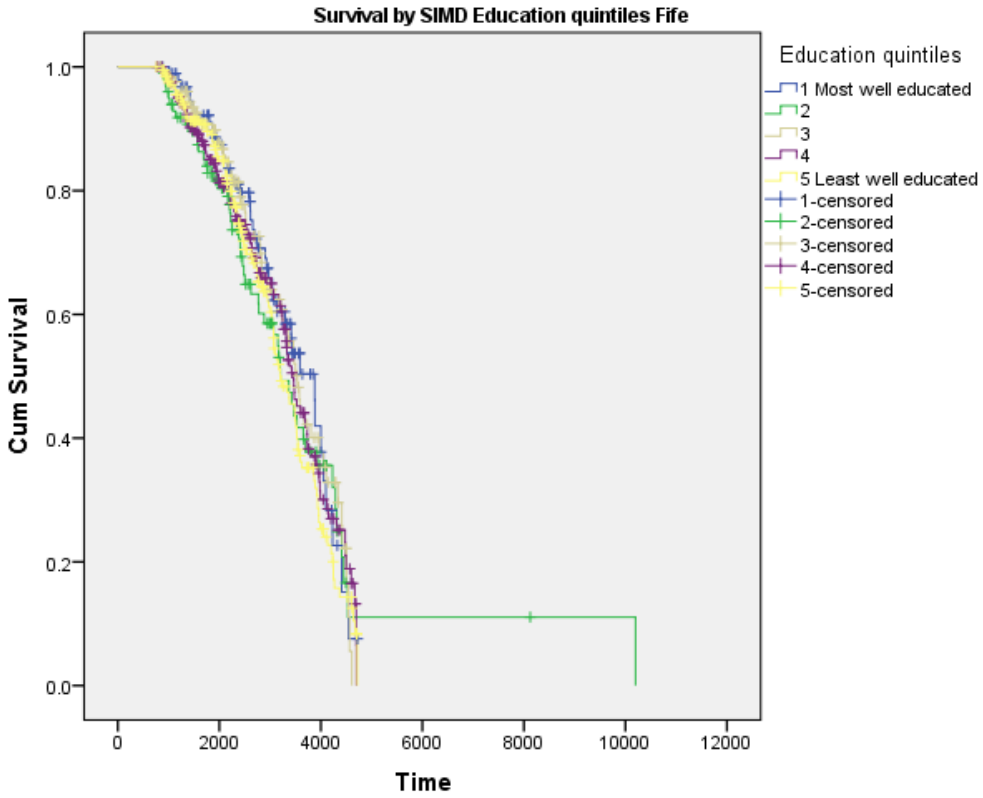
Survival distributions classified by Scottish SIMD quintiles (Figure 25) were the next step and we found that the fifth quintile (least deprived) appeared to have a much higher survival with mean survival of 3573.006 days compared to the Quintile 4 with the worst mean survival time of 2.994.637 days. The cumulative survival distribution reached statistical significance with a value of p=0.027 and χ^2 of 10.976.

Figure 25 Fife survival distributions by SIMD quintiles



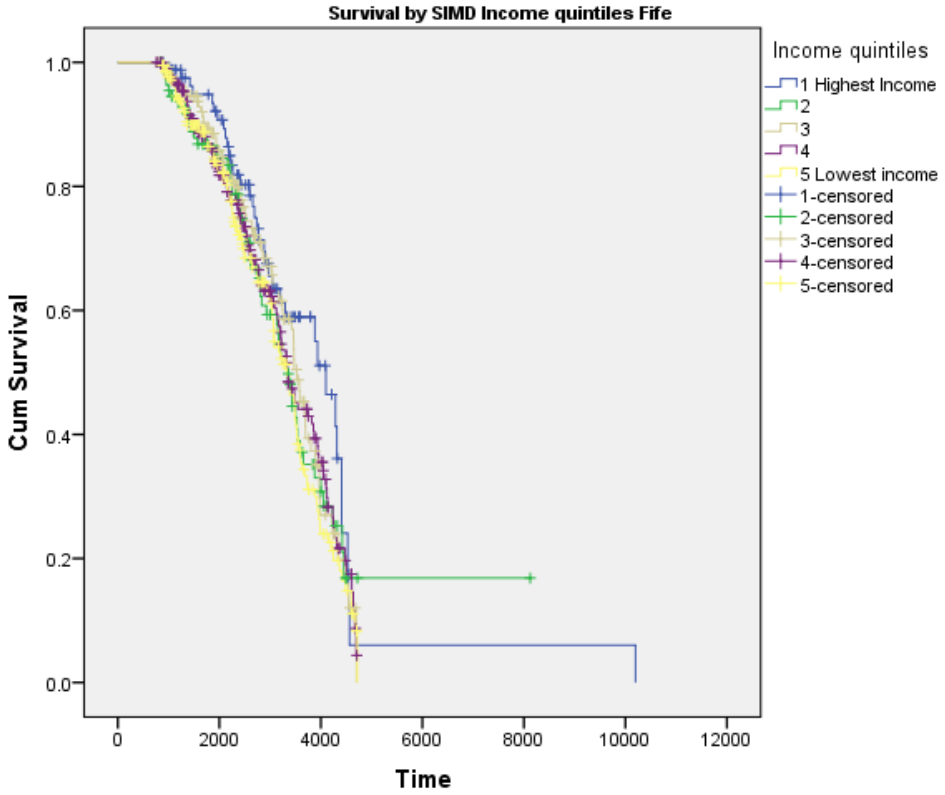
A log rank test was run to determine if there were differences in the survival distribution for the SIMD Education quintiles. The cumulative survival distribution (Figure 26) did not reach statistical significance with a value of 0.653 and χ^2 of 2.451.The fifth quintile (least well educated) appeared to have a much lower mean survival of 3190.224 days compared to Quintile 2 with 3797 days.

Figure 26 Survival distribution by Education quintile Fife



Cumulative survival for all SIMD Income groups (Figure 27) did not reach statistical difference between the groups with χ^2 of 4.345 and a p value=0.361. In terms of the cumulative survival distribution of patients from Quintile 5 (lowest income group) appeared to have the lowest cumulative survival proportion 3164.602 days compared to Quintile 1 (highest income groups) who had cumulative survival of 3903.894 days.

Figure 27 Survival distribution by SIMD Income quintile Fife



As the initial exploration of the data using Kaplan-Meier was complete, the next step was to conduct an analysis of time to death determined by the key predictors, comorbidity and SES.

6.2.3. Cox proportional hazards regression - Fife dataset

The Cox proportional hazards regression was used as it is the ideal method to estimate the relative risk of death within the cohort. The first model was an unadjusted Cox regression using just SES and comorbidity. The initial model fit was tested using the survival package in R to ensure the assumptions of the model had been met. This would allow for more precise estimates of prognostic effect of both comorbidity and SES.

Table 22 Initial Cox Model of SIMD and CCI

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Most deprived SIMD quintile (Ref group)	4	.029			
SIMD quintile 2		.211	.832	.625	1.109
SIMD quintile 3		.539	.912	.680	1.123
SIMD quintile 4		.217	1.231	.885	1.713
Least deprived SIMD quintile		.019	.646	.449	.930
CCI No comorbidity (Ref group)	3	.049			
CCI Mild comorbidity		.431	.829	.519	1.323
CCI Moderate comorbidity		.574	.913	.664	1.255
CCI Severe comorbidity		.151	1.233	.926	1.642

The individual predictors of Scottish SIMD quintiles and CCI were placed in the model (Table 22), and they were unable to demonstrate a reduction in survival. We repeated the analysis substituting CCI with ECI score. For SIMD quintiles there appeared to be a protective effect for patients from Quintile 5 (Least deprived) as the hazard of 0.655 reached statistical significance with p=0.023. There was evidence of a doubling of the risk (HR=2.283, p=0.023) when comparing the survival of patients without comorbidity to those with severe comorbidity as measured using the ECI. We conducted the same analysis but this time we used SIMD Income and Education quintiles to approximate SES with CCI for comorbidity. This regression analysis found a marginally statistically significant reduction in survival for severe comorbidity with HR=1.3336, p=0.051 (95%CI 0.999-1.787). When this analysis was repeated using ECI to measure comorbidity, there was a marked decrease in survival for severe comorbidity with HR=2.229 and this reached statistical significance with p=0.027 (95%CI 1.096-4.533).

As a next step within the analysis, Cox Proportional Hazards Regression Model that adjusted for the following variables of interest age, sex, stage, smoking and alcohol status was conducted. The Cox model appeared to show that when compared to the most deprived group, patients from the least deprived quintile had an increase in survival with reduced risk of death of nearly 30% but this result did not attain statistical significance.

A comparative model using the ECI instead of CCI demonstrated a survival effect for moderate comorbidity with a hazard ratio of 1.465 which reached statistical significance with p=0.046 (95% CI 1.007-2.131). Using income and education alongside CCI, we were unable to demonstrate an effect on survival as the results did not reach statistical significance. Another subsequent model using ECI for comorbidity status, and income and education for SES, did not find a survival effect. Moderate comorbidity did show promise but despite risk of death reaching marginal statistical significance with p=0.053 and HR=1.450, the null hypothesis could not be rejected as the 95% CI included 1.

Our next attempt was to fit a model that adjusted for Scottish SIMD quintiles, CCI, HNC type, age and stage. This model did not appear to show an effect on survival as the 95% confidence intervals for the hazard ratios included 1. Replacing CCI with ECI did not show any effect (Table 23), however moderate comorbidity showed a significant survival disadvantage as it nearly showed effect with HR=1.452, p=0.051 but the lower limit of the 95% CI was 0.999 which is less than 1 therefore the null hypothesis could not be rejected.

Table 23 Cox Model HNC type, stage, age, + Scottish SIMD and ECI

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Most deprived SIMD quintile (Ref group)	4	.209			
SIMD quintile 2		.213	.782	.531	1.151
SIMD quintile 3		.662	.911	.602	1.380
SIMD quintile 4		.251	1.311	.817	2.169
Least deprived SIMD quintile		.208	.718	.428	1.203
ECI No comorbidity (Ref group)	3	.268			
ECI Mild comorbidity		.783	1.005	.719	1.549
ECI Moderate comorbidity		.051	1.452	.999	2.111
ECI Severe comorbidity		.867	.905	.279	2.929

Using CCI alongside the income and education quintiles was able to demonstrate a statistically significant reduction of survival in the cohort but this was only apparent for patients with severe comorbidity compared to those without comorbidity, HR=1.744, p=0.045 (95%CI 1.013-3.005).

After repeating the analysis using a model that used ECI in the place of CCI, no effect on survival was observed.

In the next proportional hazards regression model, we decided to drop age as a separate predictor from the analysis as it was possible there was some interaction with CCI as it was the age=related CCI that which used to calculate the summary comorbidity score. In spite of the changes, the new iteration did not show that either comorbidity or SES measured using the CCI and Scottish SIMD quintiles respectively were good predictors of survival as they continued to show no significant effect (Table 24).

Table 24 Cox Model HNC type, Stage +Scottish SIMD +CCI

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Most deprived SIMD quintile (Ref group)	4	.289			
SIMD quintile 2		.189	.772	.525	1.136
SIMD quintile 3		.830	.956	.634	1.442
SIMD quintile 4		.381	1.234	.771	1.973
Least deprived SIMD quintile		.249	.739	.443	1.235
CCI No comorbidity (Ref group)	3	.028			
CCI Mild comorbidity		.216	.622	.294	1.319
CCI Moderate comorbidity		.942	.981	.595	1.619
CCI Severe comorbidity		.192	1.366	.855	2.183

Comparing the same variables and using ECI in place of CCI showed a measure of effect for ECI measured comorbidity, particularly moderate comorbidity, HR= 1.478 (p=0.040). Running a new Cox regression model that used SIMD income and education quintiles instead of SIMD quintiles alongside CCI could not demonstrate an effect on survival. However the one that substituted ECI for CCI and had SIMD income and education for SES, found an effect survival for patients with moderate comorbidity. Survival wamelike a hazard of 1.525 which reached statistical significance with p=0.031, (95%CI 1.039-2.239). Multivariate analysis adjusting for HNC type and disease stage did not demonstrate a survival effect for ECI measured comorbidity, although the hazard ratios increased from 0.610 for mild comorbidity to 1.374 for severe comorbidity.

We ran another Cox regression model and substituted SIMD income and education quintiles to take the place of SIMD and used the CCI score for comorbidity. The results were unable to demonstrate an effect on survival. After using ECI in place of CCI in a subsequent model, this showed an effect only for moderate comorbidity, with HR=1.560, p=0.023 (95%CI 1.064-2.288). In order to elicit whether comorbidity and SES were linked to survival in our cohort of patients we ran two regression models where comorbidity was measured using first the CCI and SES using the SIMD income and education quintiles. This analysis was able to demonstrate an increasing risk of death based on both SES and comorbidity (Table 25) as there was a two-fold increase in risk of death (p=0.040) when comparing severe comorbidity to not having any comorbidity. In terms of SES, there was a less clear measure of association for both SIMD income and education with death.

Table 25 Cox Model of All variables + CCI + SIMD income and education

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
CCI No comorbidity (Ref group)	3	.024			
CCI Mild comorbidity		.867	.922	.358	2.378
CCI Moderate comorbidity		.502	1.283	.620	2.654
CCI Severe comorbidity		.040	2.117	1.037	4.325
Lowest Income quintile (Ref group)	4	.901			
Income quintile 2		.421	.682	.268	1.733
Income quintile 3		.590	.748	.260	2.151
Income quintile 4		.445	.654	.220	1.945
Highest Income quintile		.656	.768	.240	2.457
Most educated quintile (Ref group)	4	.446			
Education quintile 2		.376	1.511	.606	3.767
Education quintile 3		.789	.879	.342	2.259
Education quintile 4		.741	1.180	.443	3.145
Least educated quintile		.674	.792	.267	2.349

The same model using the ECI measured comorbidity had contrasting results to the CCI model as depicted in Table 27. In this model moderate comorbidity had a nearly two-fold higher risk of death than no comorbidity. This result was highly statistically significant with p=0.014. Level of income had a protective effect. In the education quintiles the analysis appeared to show that

patients from Quintile 2 had 1.3 times the risk of death compared to the least well educated group.

Table 26 Cox Model of All variables + ECI + SIMD income and education

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
ECI No comorbidity (Ref group)	3	.053			
ECI Mild comorbidity		.951	.983	.560	1.723
ECI Moderate comorbidity		.014	1.960	1.143	3.362
ECI Severe comorbidity		.276	.439	.100	1.931
Lowest Income quintile (Ref group)	4	.975			
Income quintile 2		.783	.875	.337	2.268
Income quintile 3		.553	.716	.237	2.162
Income quintile 4		.655	.773	.250	2.392
Highest Income quintile		.766	.835	.255	2.736
Least educated quintile (Ref group)	4	.654			
Education quintile 2		.521	1.349	.540	3.371
Education quintile 3		.755	.858	.329	2.239
Education quintile 4		.753	1.176	.429	3.226
Most educated quintile		.788	.859	.285	2.595

A final model was run that adjusted for all the following predictor variables, smoking and alcohol status, HNC Type, stage, alongside the prognostic variables namely SIMD income and education quintiles as well as CCI and ECI. The rationale for the use of both the CCI and ECI in the model to check if there was an increase in the parameter estimates. This model showed that moderate and severe comorbidity measured using ECI were able to demonstrate a marked reduction in survival when compared against the no comorbidity category. The results of this analysis are shown in Table 27. Mild ECI comorbidity had a pronounced impact on survival although this result was marginally insignificant with risk of death 4 times that of patients without comorbidity, (HR=4.424, p=0.052). This pattern of poor survival prediction was also noted for ECI measured comorbidity severe comorbidity category which demonstrated a relative risk nearly 5.5 times that of patients without comorbidity, (HR=5.465 p=0.029). Comorbidity measured by CCI was shown to have no effect as all the hazard ratios were less than 1.

Table 27 Cox Model of All variables + SIMD Income, Education + ECI + CCI

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
ECI No comorbidity (Ref group)	3	.033			
ECI Mild comorbidity		.052	4.424	.988	19.810
ECI Moderate comorbidity		.262	2.356	.527	10.527
ECI Severe comorbidity		.029	5.465	1.190	25.086
CCI No comorbidity (Ref group)	3	.002			
CCI Mild comorbidity		.008	.372	.180	.771
CCI Moderate comorbidity		.009	.350	.158	.772
CCI Severe comorbidity		.002	.461	.284	.748
Lowest Income quintile (Ref group)	4	.763			
Income quintile 2		.556	1.400	.456	4.293
Income quintile 3		.995	1.003	.397	2.535
Income quintile 4		.422	.757	.383	1.495
Highest Income quintile		.831	.943	.552	1.611
Most educated quintile (Ref group)	4	.354			
Education quintile 2		.886	1.079	.382	3.050
Education quintile 3		.656	1.232	.493	3.078
Education quintile 4		.642	.825	.367	1.855
Least educated quintile		.133	1.505	.883	2.567

6.2.4. Results of Multiple Imputations in Fife dataset

It was noted from this analysis that 586 patients representing 66.9% of the cohort would have been dropped from the analysis due to missing values. From this it was deemed necessary to conduct multiple imputation methods to fill in the missing values. Conditional imputation was employed and the output of the different analyses is presented. Linear dependency prevented the analysis of CCI and Scottish SIMD quintiles as predictors. An imputation model was run but this could not generate pooled data. Similar issues were observed for SIMD income and education quintiles when they were included in a multivariate model.

A multiple imputation (MI) model of ECI and Income and Education domains was conducted. The pooled data showed a reduction in the standard errors compared to the original data. There did not appear to be any effect in predicting survival from the imputed variables to demonstrate an effect of comorbidity and SES on survival. Similar imputations were run for the rest of the analyses incorporating the different combinations of explanatory variables using either CCI or ECI for comorbidity and Scottish SIMD quintiles or income and education domain scores to approximate SES. The outputs for these analyses using the imputed data are depicted in the ensuing analyses.

Table 28 Cox Model of Age, Smoking, Alcohol, Income, Education and ECI with MI data

Explanatory variables	Sig	HR	95% CI for HR	
			Lower	Upper
Income Quintile 2	.227	.198	1.339	.858
3	.292	.278	1.373	.773
4	.303	.305	1.365	.753
Lowest Income quintile	.315	.141	1.591	.858
Education Quintile 2	.237	.646	1.115	.700
3	.295	.845	.944	.525
4	.311	.659	.871	.471
Least educated Quintile	.316	.843	.939	.504
ECI Mild comorbidity	.164	.413	1.144	.828
ECI Moderate comorbidity	.160	.959	.992	.724
ECI Severe comorbidity	.375	.023	2.353	1.128

A model that used age, smoking, alcohol, SIMD income and education quintiles and ECI did not demonstrate a clear increase in risk of death in the imputed data compared to the original data (Table 28), however this changed in the subsequent analysis model using imputed data, with evidence of a gradient in survival being particularly apparent for alcohol status, smoking status, ECI, income and education quintiles. There was no clear pattern of approximating survival for the predictors, age, smoking, alcohol, SIMD income and education quintiles and ECI within the model (Table 29) which was unexpected after the addition of stage to the same predictors as those in the previous model.

Table 29 Cox Model of HNC Type, Income, and Education, stage, alcohol, smoking and ECI with MI data

Explanatory variables	Sig	HR	95% CI for HR	
			Lower	Upper
Education Quintile 2	.241	.702	1.097	.683
3	.282	.853	1.054	.605
4	.306	.905	.964	.527
Least educated quintile	.317	.792	1.087	.583
Income Quintile 2	.235	.299	1.277	.805
3	.321	.699	1.133	.598
4	.352	.585	1.213	.598
Lowest Income quintiles	.345	.473	1.282	.648
ECI Mild comorbidity	.259	.081	1.571	.945
ECI Moderate comorbidity	.229	.178	1.364	.868
ECI Severe comorbidity	.171	.248	1.219	.871

When analysing the original Fife data, we had conducted a multivariate Cox model with both comorbidity measures but excluding age. Therefore, we replicated this same step within the dataset with imputed values for the missing data. We wanted to investigate whether using both ECI and CCI (Table 31) alongside the other predictor variables would make a difference to the risk modelling conducted thus far as previous models that included CCI had been unable to estimate the magnitude and direction the of effect on survival due to issues of co-linearity and failure of coefficient convergence. We found that using both measures of comorbidity improved the risk attenuation in the entire model.

Table 30 Final Cox Model of HNC Type, education, income, age, stage, CCI with MI data

Explanatory variables	Sig	HR	95% CI for HR	
			Lower	Upper
Education Quintile 2	.244	.648	1.118	.692
3	.285	.819	1.068	.609
4	.312	.982	1.007	.544
Least educated quintile	.322	.714	1.125	.597
CCI Mild comorbidity	.277	.992	.997	.579
CCI Moderate comorbidity	.219	.824	1.050	.676
CCI Severe comorbidity	.200	.032	1.542	1.038
Income Quintile 2	.238	.449	1.197	.751
3	.330	.751	1.111	.574
4	.358	.736	1.129	.549
Lowest Income quintiles	.359	.649	1.179	.577

6.3.1. Tayside Cohort

The Tayside cohort consisted of 468 patients who were included in the analysis, including 320 males (68.4%) and 148 females (31.6%). The largest age group were patients were aged between 61 and 70 years (34.4%), followed by those over 71 who made up 31.4% (n=147) of the cohort. Heavy smokers made up 34% of the cohort, and 23.3% of patients were classed as hazardous drinkers. The types of HNC subsite included 29.7% for mouth and 26.6% for laryngeal cancer. Most of the patients were in stage IV (38.5%) and 21.2% patients were in stage I with the rest distributed over the other disease stages. Over three quarters of the patients had a CCI score of moderate comorbidity or severe comorbidity with both categories making up 38.7% and 40.6% respectively. The ECI score of no comorbidity had a 66.7% share of the cohort while only 31 patients were classed as having moderate comorbidity and 7 patients had an ECI score of severe comorbidity.

6.3.2. Results of Kaplan-Meier Analysis in Tayside dataset

The cumulative survival distributions were conducted for the Tayside cohort. The first variable to be evaluated was age, however prior to this we checked to see if there was a pattern in the distribution of ECI based on the patients' ages, prior to conducting the Kaplan-Meier survival analysis.

Table 31 Cross tabulation of Age and ECI

		ECI				Total
		None	**Mild**	**Moderate**	**Severe**	
Age Group	**<40 years**					
	41-50 years	7	0	0	0	7
	51-60 years	24	0	0	0	24
	61-70 years	80	8	10	2	100
	71+ years	107	20	9	3	139
Total		93	21	12	2	128

It appeared that there were more patients in the no comorbidity category (Table 31). Of note was that for the mild and moderate categories there were more patients in these categories as the ages increased. In comparison the CCI and age cross tabulation (Table 32) was different as there were fewer patients in the no comorbidity and mild comorbidity categories. These two levels of comorbidity, i.e. none/mild were combined as they had only 28 (7=none, 21=mild) patients within them.

Table 32 Cross tabulation of Age and CCI

		CCI				Total
		None/Mild	**Moderate**	**Severe**	**Missing**	
Age Group	**<40 years**	7	0	0	3	10
	41-50 years	20	2	2	7	31
	51-60 years	0	83	17	17	117
	61-70 years	0	96	43	22	161
	71+ years	0	0	128	19	147
Total		27	181	190	68	466

In terms of the survival distribution by stage and Scottish SIMD, we found a trend that the majority (n=147) of patients had Stage IV disease with a larger proportion of these patients coming from quintiles 4 and 5 (Table 33).

Table 33 Cross tabulation of Disease Stage and Scottish SIMD quintiles

		Scottish SIMD Quintiles					Total
		1	2	3	4	5	
Stage	**Stage 0**	5	10	7	6	7	35
	Stage I	9	17	14	23	17	80
	Stage II	15	9	14	14	6	58
	Stage III	14	10	10	16	6	56
	Stage IV	32	25	24	46	20	147
Total		75	71	69	105	56	376

In terms of the distribution of disease stage by SIMD income quintiles, there appeared to be higher frequencies of stage IV disease in patients across all quintiles (Table 34).

Table 34 Cross tabulation of Disease stage and Income quintiles

		Scottish SIMD Income Quintiles					Total
		1	2	3	4	5	
Stage	**Stage 0**	5	10	5	6	10	36
	Stage I	16	20	15	21	14	86
	Stage II	11	6	14	16	13	60
	Stage III	8	17	7	8	17	57
	Stage IV	27	41	20	27	36	151
Total		67	94	61	78	90	390

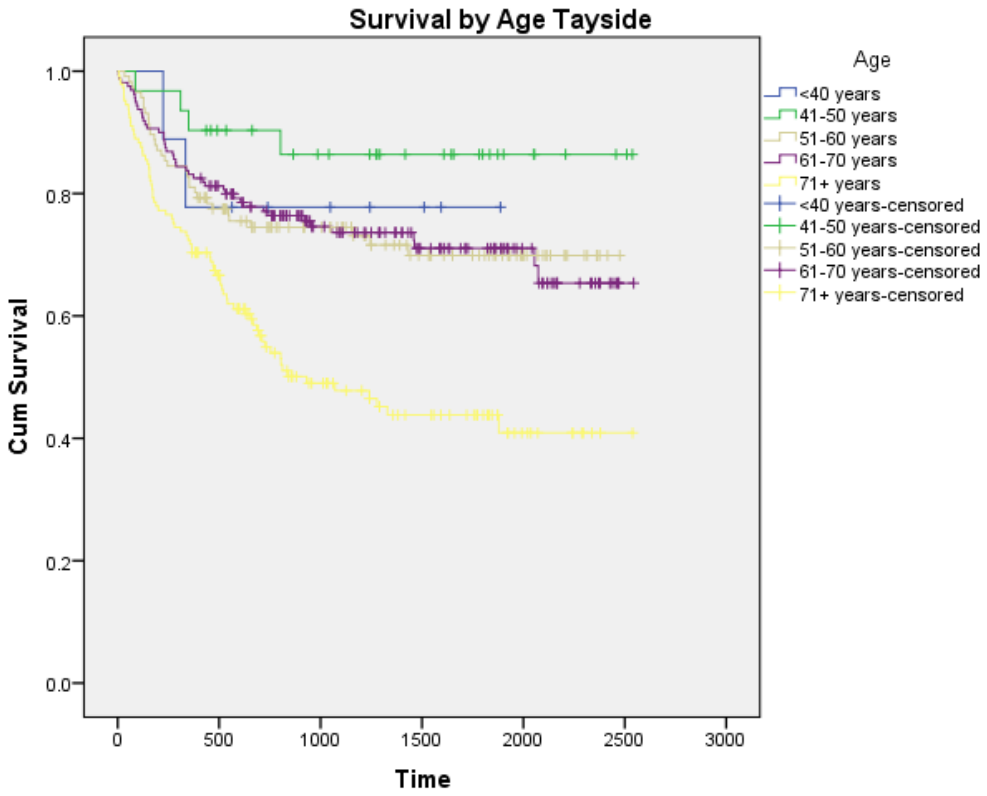
When we reviewed stage and SIMD income domain scores (See Table 34), we found similar findings to that of the Scottish SIMD quintiles. Table 36 shows this to be the same for the cross tabulation of stage and SIMD education quintiles.

Table 35 Cross tabulation of Disease stage by Education quintiles

		Scottish SIMD Education Quintiles					Total
		1	2	3	4	5	
Stage	**Stage 0**	6	6	9	7	8	36
	Stage I	17	20	17	18	14	86
	Stage II	8	10	12	11	19	60
	Stage III	8	13	14	9	13	57
	Stage IV	21	45	24	31	30	151
Total		60	94	76	76	84	390

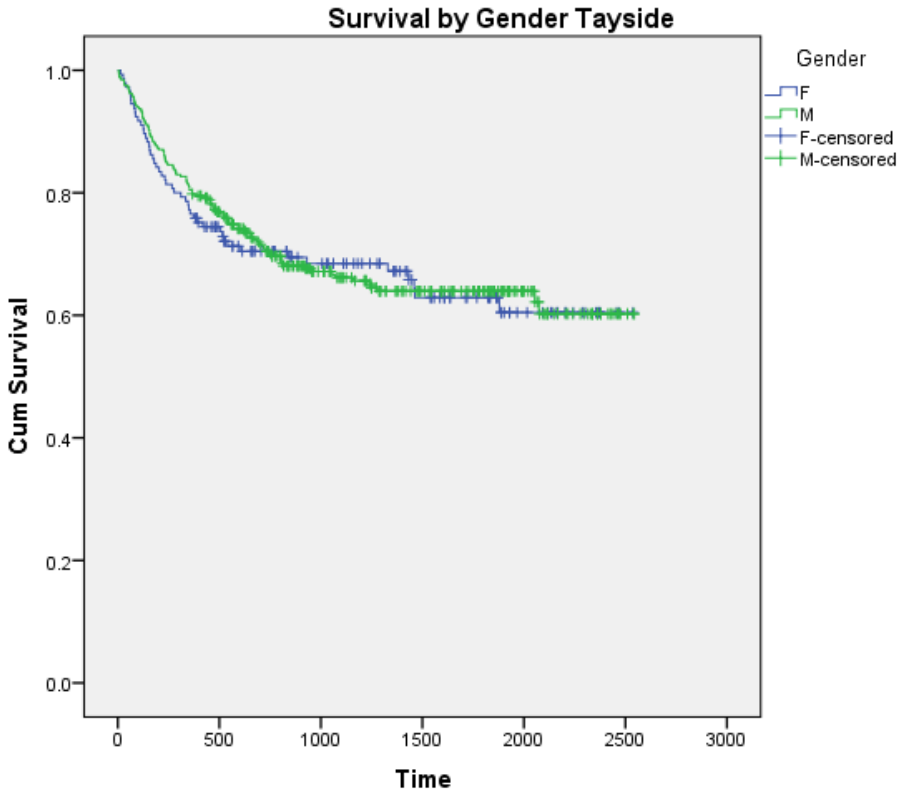
The probability of surviving dependent on age was examined and older patients had higher risk of death compared to their younger counterparts as depicted in Figure 28. The majority of the patients died within the first five years and older patients aged 71 years and older appeared to have the worst survival (1339.626 days) as an age related gradient in survival is apparent from 41 years onwards. The age group of those 41-50 years had better survival with 2248.349 days. The age related survival distribution was highly statistically significant with evidence of differences between age groups defined by χ^2 of 33.032 (p<0.0001).

Figure 28 Survival by Age group Tayside



When considering survival based on gender (Figure 29), the log rank test did not find any statistically significant differences between the two groups, χ^2 = 0.047 (p=0.829) although the survival curve appeared to indicate that being males had better survival. The mean survival times supported these results as the mean survival times for males were marginally different to females at 1761.854 days compared to 1744.859 days respectively.

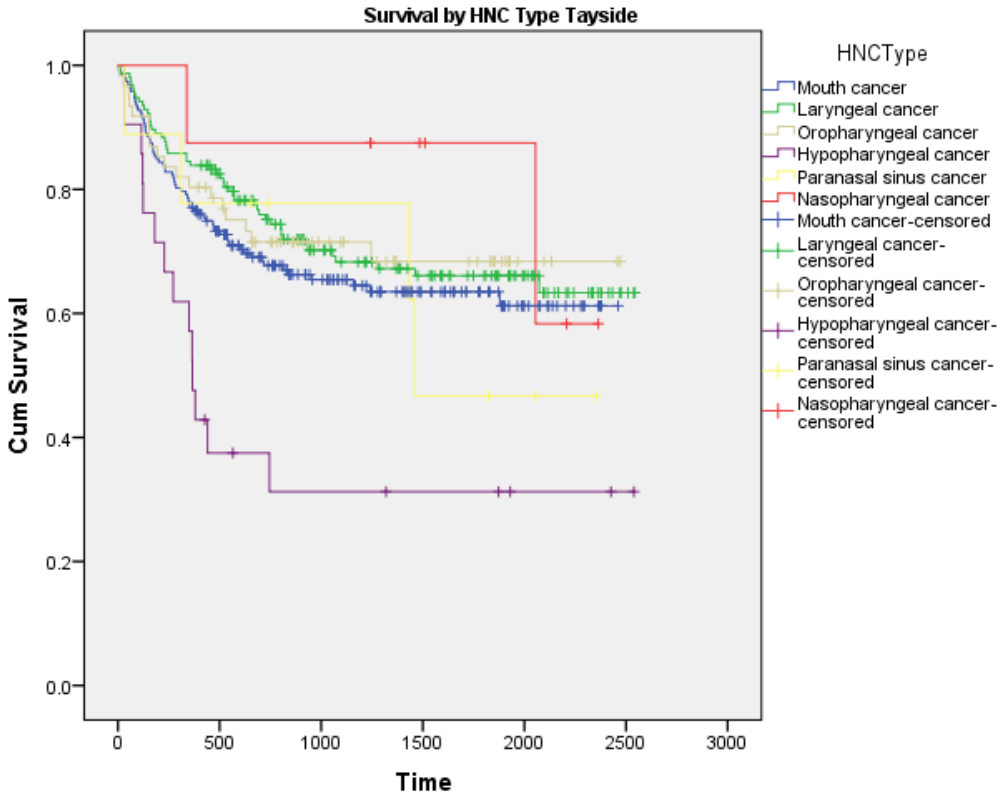
Figure 29 Survival by gender Tayside



There were more male deaths 107 (22.8%) deaths compared to 49 (10.5%) in females over the same time period, but as the male to female ratio was approximately 2:1 these findings are not surprising.

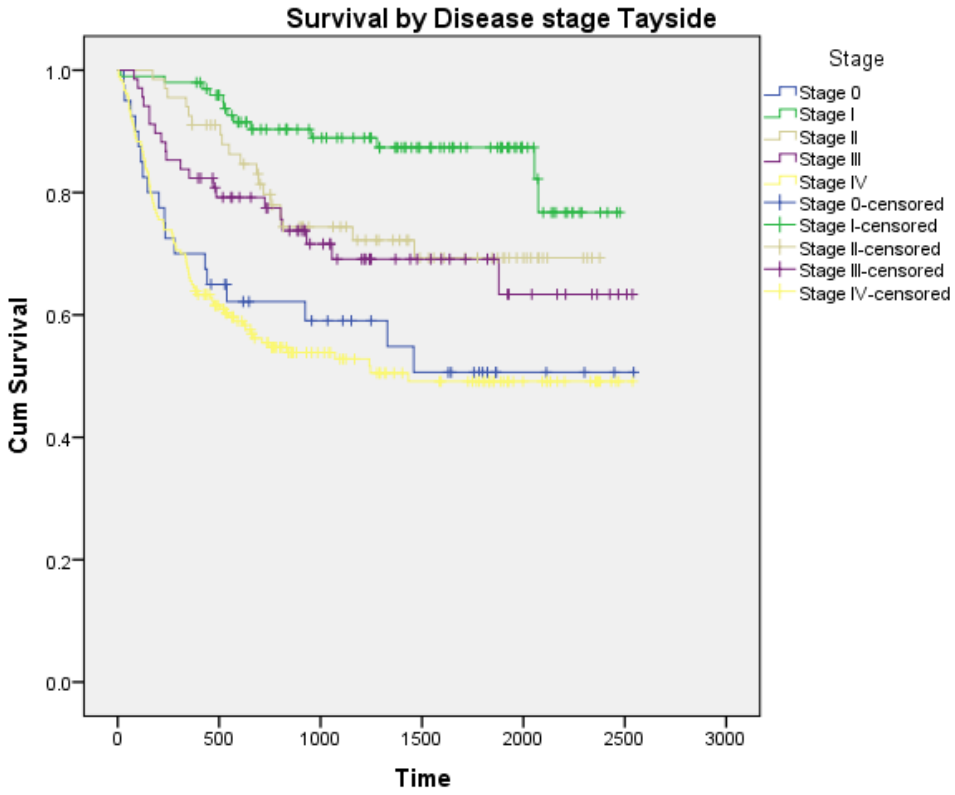
In terms of HNC type (Figure 30), the log rank test found statistically significant differences in the survival, with $\chi^2 = 16.987$ with a p.value of 0.005. Hypopharyngeal cancer was noted to have the worst survival at 985.673 days compared to the other forms of HNC. The patients diagnosed with cancers of the nasopharynx had the best survival rates at 2020.625 days.

Figure 30 Survival distribution by HNC type Tayside



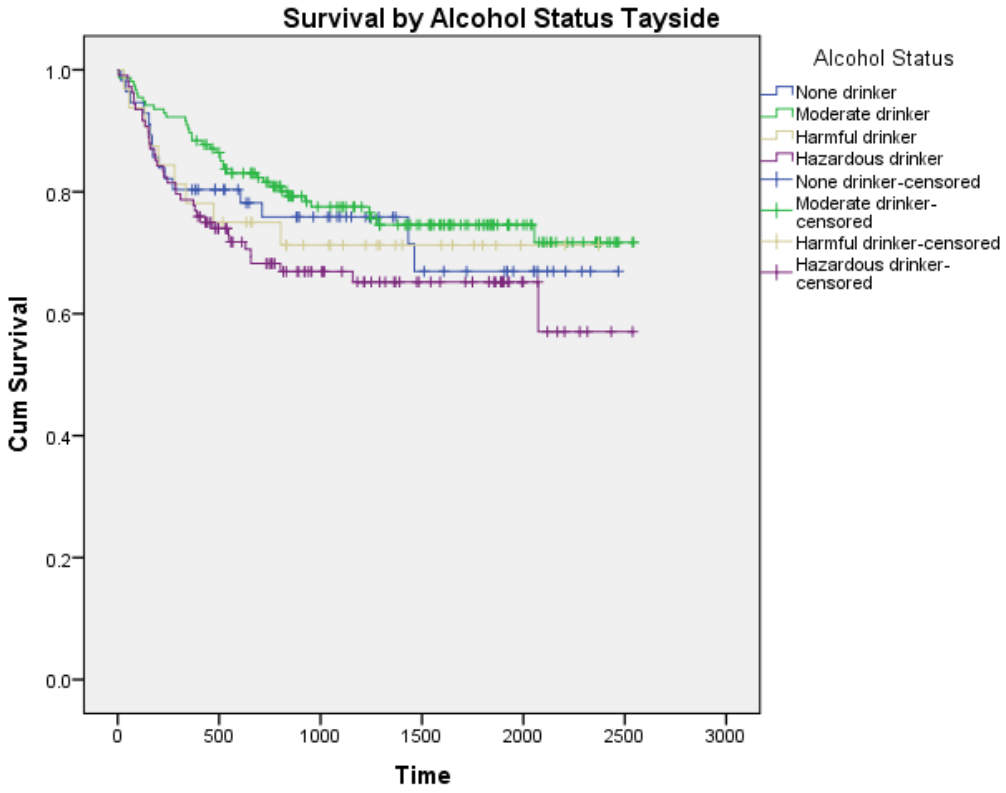
Survival distributions by disease stage (Figure 31) appeared not to follow the expected pattern of worse outcomes for increasing severity of disease. Stage 1 patients appeared to survive longer than any other patient group. The group with the worst overall survival was stage 4 disease surviving up to a mean of 1429.393 days but there was little difference with Stage 0 patients. Stage 1 patients had the best mean survival rate of 2195.024 days. The log rank test had evidence of highly statistically significant differences between the groups with χ^2 of 44.977 and p<0.0001.

Figure 31 Survival by Disease stage Tayside



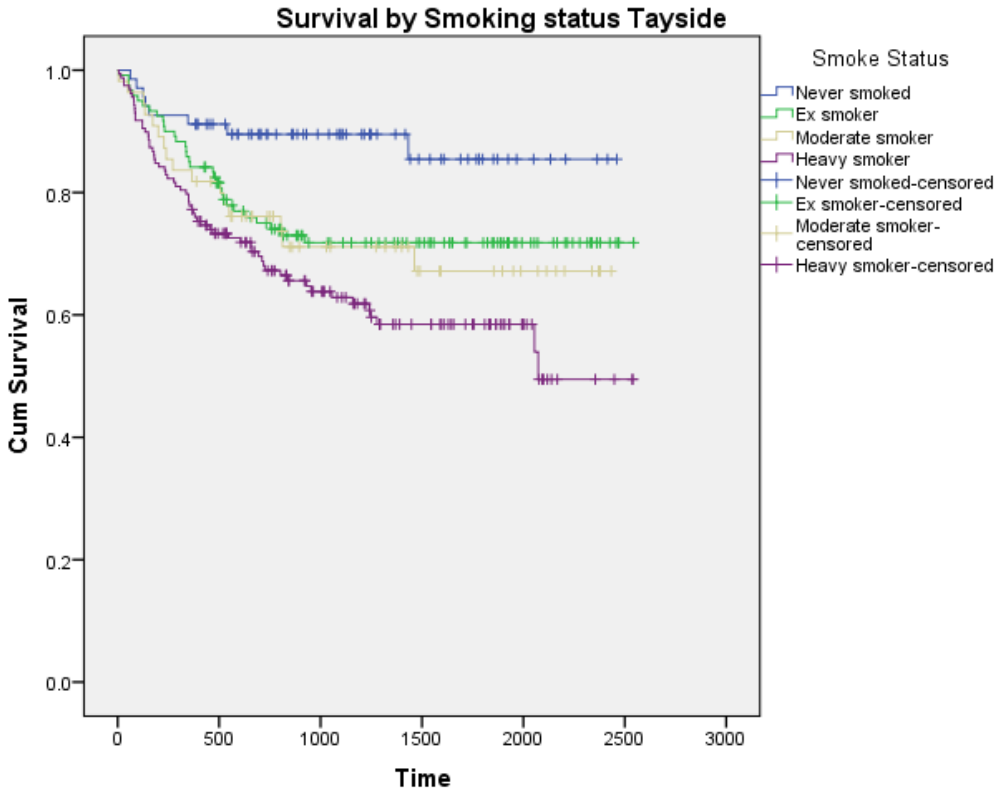
A log rank test was run to determine if there were differences in the survival distribution for the different alcohol status groups. Hazardous drinkers appeared to have the worst survival with mean survival compared to the other groups with mean survival of 1735.148 days. The cumulative survival distribution for alcohol status did not reach statistical significance, $\chi^2 = 4.608$, p=0.203 (Figure 32), with moderate drinkers appearing to have much better survival compared to the other groups with a mean survival of 2014.195 days.

Figure 32 Survival by Alcohol status Tayside



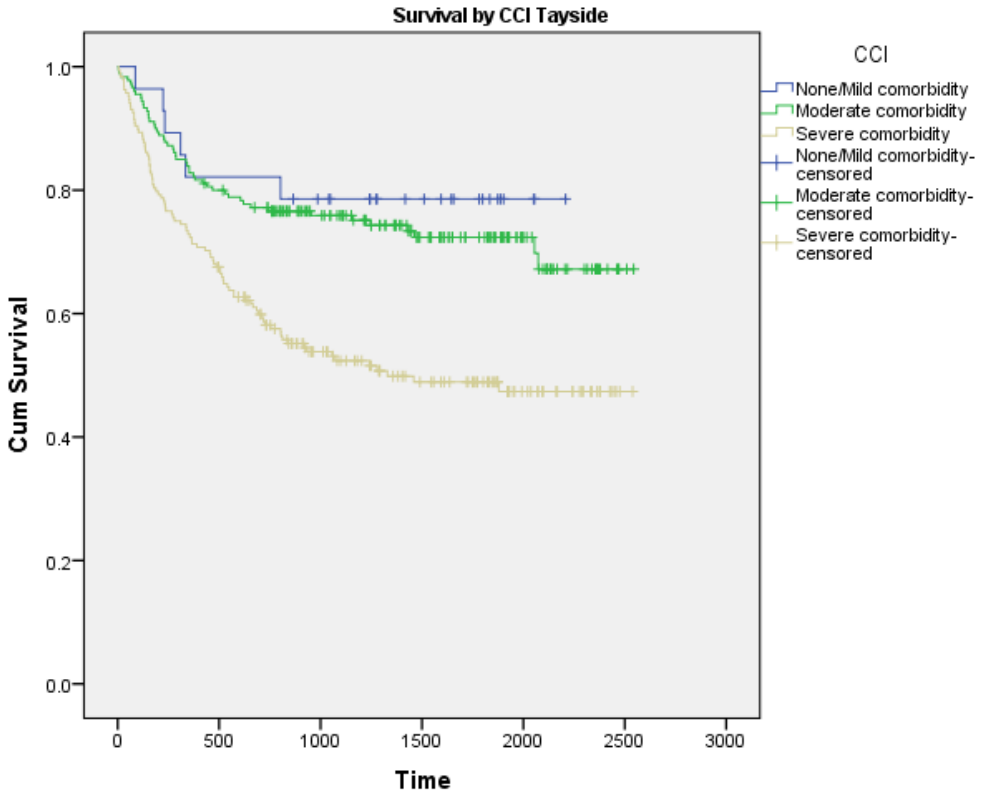
In terms of smoking status (Figure 33), non-smokers and ex-smokers had the superior outcomes compared to the other smoking groups. Mean survival rates were 1631.218 days for heavy smokers who had the worst cumulative survival and 2183.709 days for never smokers with the best outcomes. This survival distribution reached statistical significance with χ^2 test result of 15.578 ($p<0.001$).

Figure 33 Survival by Smoking status Tayside



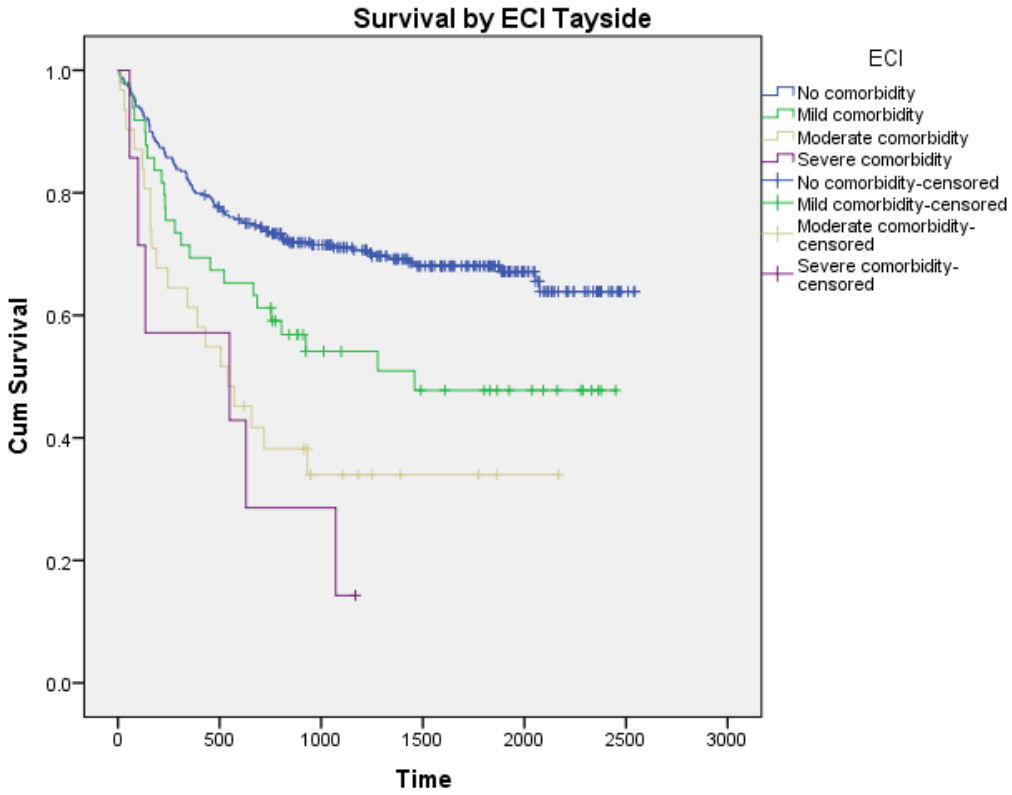
Next we decided to test the survival distribution in terms of the survival as determined by comorbidity status measured using the CCI (Figure 34). We found that the survival experiences of the Tayside patients were difficult to unravel as a lot of events occurred across all comorbidity levels. The mean and median survival times showed that patients with moderate comorbidity had the best outcomes compared to severe comorbidity group with mean survival of 1932.934 days and 1448.493 days respectively. This cumulative survival analysis achieved statistical significance with χ^2 of 22.020, $p<0.0001$.

Figure 34 Survival by CCI Tayside



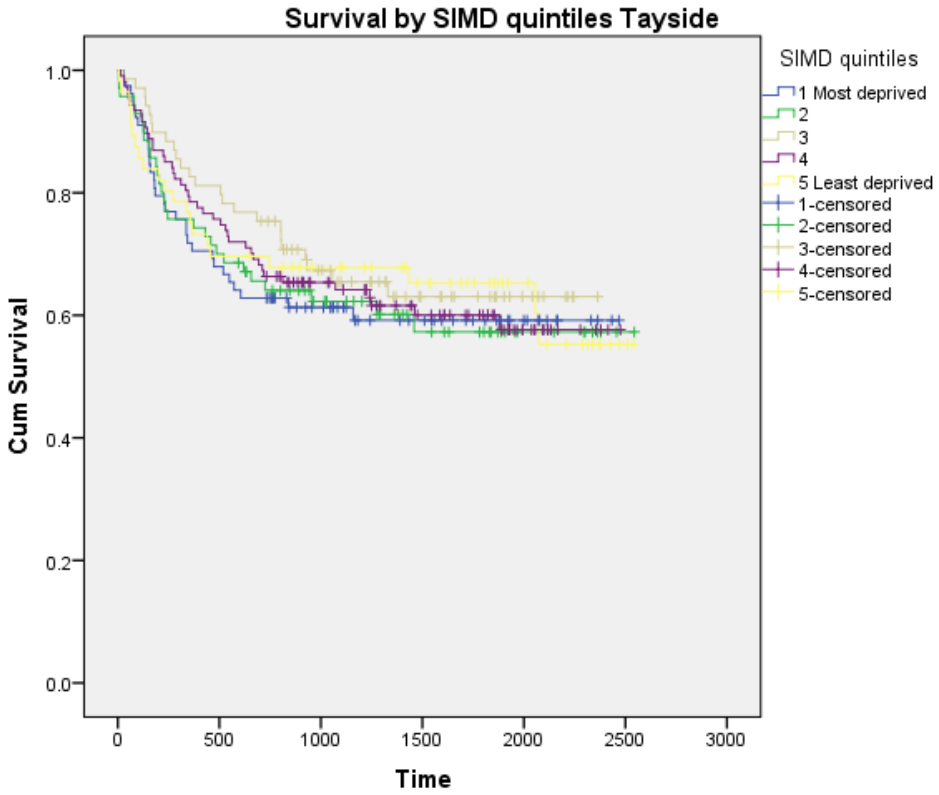
When assessing the survival distribution of comorbidity using ECI (Figure 35) was taken into account to estimate the survival of patients in the cohort, severity of comorbidity was shown to be linked to poorer survival. A log rank test was run to determine whether there were differences in the survival distribution for ECI, and they were statistically significantly different with χ^2 score of 31.845 with a p value <0.0001. Patients classed as having severe comorbidity had a mean survival of 530 days while the best survival times were for patients without any comorbidity at 1842.576 days.

Figure 35 Survival distribution by ECI Tayside



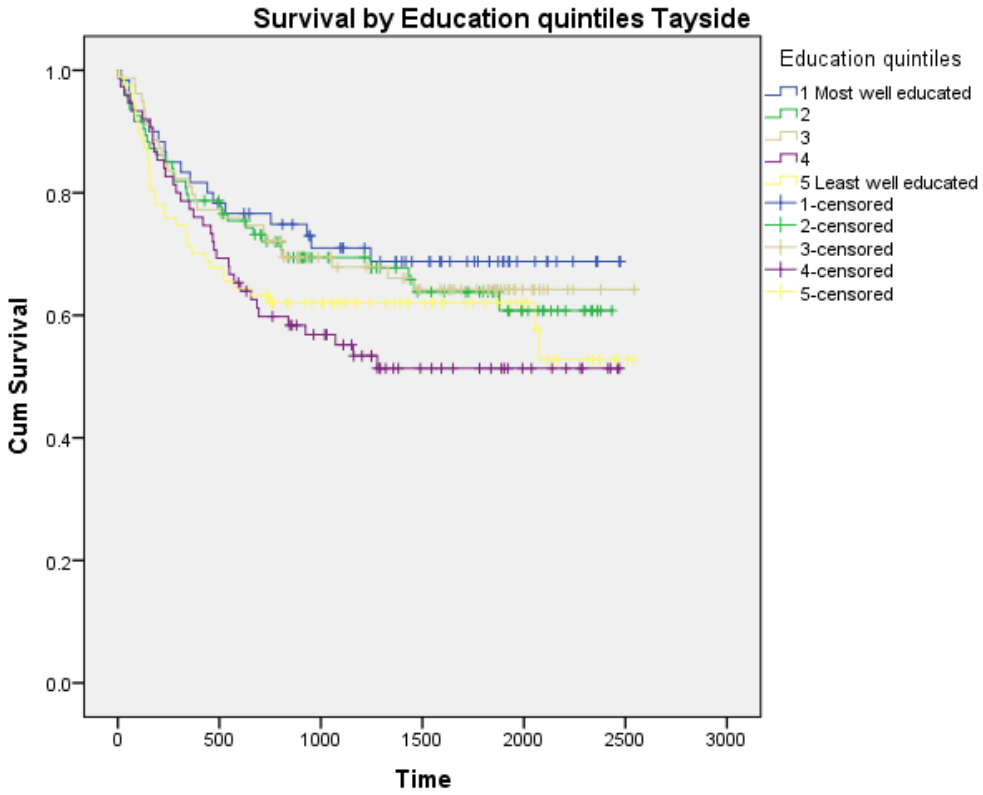
Cumulative survival estimates were conducted based on SES using the SIMD quintiles (Figure 36) and it was apparent that an inverse relationship existed with quintile 1 patients having worse survival. The log rank test did not show evidence of statistically significant differences between groups, with $\chi^2 = 1.028$ (p=0.906). We were however able to determine that patients from the most deprived category had lower survival (1590.289 days) and the least deprived fared better with a mean survival time of 1717.805 days.

Figure 36 Survival by Scottish SIMD quintile Tayside



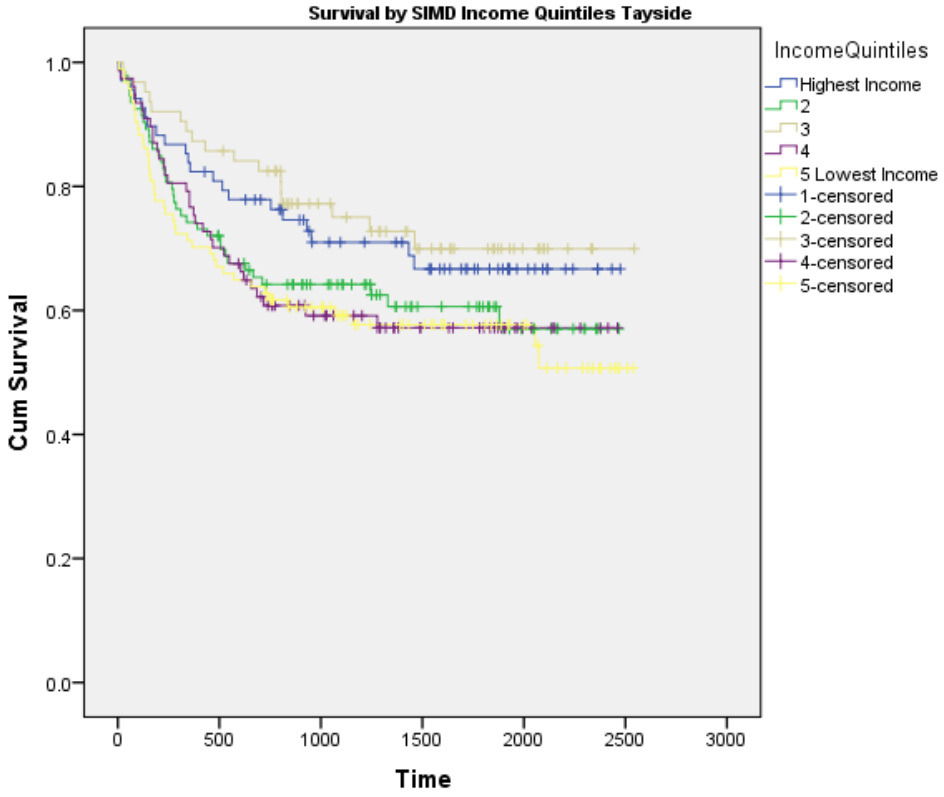
We assessed the cumulative survival distribution of SES measured using the SIMD Education quintiles (Figure 37). Although the model did not meet the statistical significance level with χ^2 = 5.024 and p = 0.285, the Kaplan-Meier curves appeared to show that Quintile 4 had the worst overall survival while the most educated (Quintile 1) had better outcomes. This finding was confirmed by the mean survival times of 1491 days and 1833.497 days for Quintile 4 and Quintile 1 respectively.

Figure 37 Survival by SIMD Education quintiles Tayside



Using SIMD income domain scores (Figure 38); we were able to determine that quintile 3 had the best mean survival compared to lowest income quintile at 1567.818 days and 1965.660 days respectively. This result, however did not reach statistical significance as χ^2 test statistic of 7.046 which had a p value of 0.133.

Figure 38 Survival by SIMD Income quintiles Tayside



6.3.3. Cox proportional hazards regression - Tayside

As the Tayside cohort information was relatively complete in comparison to the Fife data, we began by analysing the relationship between the CCI and Scottish SIMD quintiles (Table 36). Survival estimates appeared to decrease with each incremental level of comorbidity with the hazard ratios going up to nearly three times the risk of death for patients without comorbidity or those with mild comorbidity. This result achieved statistical significance with p=0.015 but there is no clear pattern of survival based on Scottish SIMD quintiles.

Table 36 Initial Cox Model of CCI and SIMD quintiles

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
CCI None/Mild (Ref group)	2	.000			
CCI Moderate		.500	1.341	.571	3.149
CCI Severe		.015	2.821	1.226	6.486
Most deprived SIMD quintile (Ref group)	4	.984			
Quintile 2		.943	.981	.588	1.637
Quintile 3		.567	.855	.501	1.461
Quintile 4		.844	.955	.600	1.519
Least deprived SIMD quintile		.820	.937	.538	1.634

Using the SIMD Income and Education domain quintiles in place of the Scottish SIMD quintiles (Table 37) showed a protective effect as the level of education was shown to increase survival when the most educated quintile was compared to the least educated quintile. The risk patterning in the income domain was less clear as Quintile 2 had a risk of HR=1.234 but this hazard ratio was not a good indicator of survival as the result did not reach statistical significance. As for the other variables in the model, these were shown to have an attenuation of risk corresponding to an increase in the hazard ratio to 2.7 times in patients with severe comorbidity compared to patients with mild or no comorbidity.

Table 37 Cox Model of SIMD income and education and CCI

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Highest Income quintile (Ref group)	4	.361			
Quintile 2		.470	1.234	.698	2.183
Quintile 3		.252	.638	.296	1.377
Quintile 4		.753	.875	.380	2.011
Lowest Income quintile		.809	.896	.368	2.182
Most educated quintile (Ref group)	4	.657			
Quintile 2		.691	1.129	.621	2.054
Quintile 3		.297	1.471	.712	3.039
Quintile 4		.139	1.909	.810	4.499
Least educated quintile		.224	1.773	.704	4.465
CCI None/Mild (Ref group)	2	.000			
CCI Moderate		.508	1.333	.569	3.125
CCI Severe		.017	2.744	1.196	6.295

In the next model (Table 38) we decided to investigate whether a model that incorporated all the variables (gender, HNC Type, smoking and alcohol status, disease stage) with SES measured by Scottish SIMD quintiles and comorbidity measured by CCI would be able to predict survival based on increasing levels of severity of comorbidity and decrease in SES. We found what appeared to be an effect on mortality risk, despite the results not reaching statistical significance. These results matched findings of the Kaplan-Meier survival curves which showed a trend of poorer survival estimates for patients from the low income backgrounds

Table 38 Cox Model of SIMD quintiles, CCI + All variables

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Most deprived SIMD quintile (Ref group)	4	.909			
Quintile 2		.354	1.383	.696	2.745
Quintile 3		.701	1.166	.532	2.557
Quintile 4		.872	1.054	.557	1.993
Least deprived SIMD quintile		.644	1.202	.551	2.620
CCI None/Mild (Ref group)	2	.004			
CCI Moderate		.423	.657	.235	1.837
CCI Severe		.439	1.505	.535	4.230

We took out the age and sex variables and reran the models but this time instead of SIMD quintiles we used SIMD income and education domains. We found that all the variables (Table

40) were showing evidence of worsening survival dependent on SES and for comorbidity; the higher comorbidity levels had worse survival outcomes.

Table 39 Cox Model of CCI + SIMD Income and education + All variables

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Lowest Income quintile (Ref)	4	.412			
Quintile 2		.843	1.088	.473	2.502
Quintile 3		.298	0.576	.204	1.629
Quintile 4		.225	0.509	.171	1.514
Highest Income quintile		.119	0.385	.116	1.278
Most educated quintile	4	.250			
2		.748	1.156	.477	2.803
3		.217	1.888	.688	5.179
4		.037	3.369	1.076	10.549
Least educated quintile		.087	3.006	.853	10.600
CCI None/Mild (Ref)	2	.003			
CCI Moderate		.459	.685	.252	1.865
CCI Severe		.359	1.582	.593	4.218

Next we decided to change the dichotomised comorbidity categories (None/Mild comorbidity) into separate categories. Our analysis focused on the effect of both ECI and SIMD quintiles in a model (Table 40). Survival estimates using SIMD quintiles were not clear; however the risk of death was noted to increase by increasing severity of comorbidity with all comorbidity categories demonstrating a statistically significant impact on survival. Notably survival showed a marked reduction due to risk of death increasing from 1.7 ($p<0.0001$) to 4 times ($p=0.001$) for mild comorbidity and severe comorbidity respectively when compared to the no comorbidity group.

Table 40 Cox Model of ECI and Scottish SIMD quintiles

Explanatory variables	Sig	HR	95% CI for HR	
			Lower	Upper
Most deprived SIMD quintile (Ref group)	.826			
Quintile 2	.617	1.142	.679	1.919
Quintile 3	.495	.828	.481	1.424
Quintile 4	.835	.952	.597	1.517
Least deprived SIMD quintile	.809	1.072	.609	1.888
ECI None (Ref group)	.000			
ECI Mild comorbidity	.028	1.676	1.059	2.652
ECI Moderate comorbidity	.000	2.941	1.801	4.802
ECI Severe comorbidity	.001	4.134	1.772	9.644

As the results we had gotten were quite similar to the systematic review findings and the Tayside survival distributions in the Kaplan-Meier curves, we thereafter decided to use the SIMD income and education quintiles as a more reliable marker for SES (Table 41) in place of the Scottish SIMD quintiles. We found that the hazard ratios had changed to demonstrate the survival effect of these variables. Income appeared to affect prognosis as it had a steady increase in risk although it is unclear why the patients in Quintile 2 had poor survival with a hazard ratio of 1.290. Although the hazard ratios for education did not attain statistical significance, education appeared to be clinically relevant as a pattern of risk is apparent with survival estimates decreasing. This is evident as hazard ratios increased from approximately 1.3 to 1.8 for the least educated compared to the well educated group. Only ECI was noted to show a consistently statistically significant increased risk of death based on presence and severity of comorbidity. Mild comorbidity was shown to predict lower survival by up 1.6 times compared to no comorbidity (p=0.033). The risk increased to 2.813 (p=0.000) for moderate comorbidity and 3.513 (p=0.003) for severe comorbidity.

Table 41 Cox Model of SIMD income and education with ECI

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Lowest Income quintile (Ref group)	4	.605			
Quintile 2		.546	1.190	.677	2.092
Quintile 3		.398	.718	.333	1.548
Quintile 4		1.000	1.000	.437	2.288
Highest Income quintile		.932	1.040	.424	2.549
Most educated quintile (Ref group)	4	.695			
Quintile 2		.399	1.290	.713	2.335
Quintile 3		.395	1.368	.665	2.813
Quintile 4		.155	1.853	.791	4.341
Least educated quintile		.355	1.549	.613	3.915
ECI None (Ref group)	3	.000			
ECI Mild comorbidity		.033	1.636	1.039	2.576
ECI Moderate comorbidity		.000	2.813	1.714	4.617
ECI Severe comorbidity		.003	3.534	1.518	8.226

After adding all the other predictors to the model (Table 42) we found that moderate comorbidity HR=3.658 (p=0.002) and severe comorbidity HR=4.236 (p=0.006) were good

predictors of survival in patients as the hazards increased from the previous model. Although Scottish SIMD quintiles gave the impression of being good indicators of survival, the relevant hazard ratios for these three variables did not reach statistical significance.

Table 42 Cox Model of ECI, Scottish SIMD, Sex, Age, HNC Type and Stage

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Most deprived SIMD quintile (Ref group)	4	.689			
Quintile 2		.216	1.554	.773	3.124
Quintile 3		.714	1.158	.529	2.536
Quintile 4		.864	.942	.478	1.859
Least deprived SIMD quintile		.871	1.070	.472	2.429
ECI None (Ref group)	3	.001			
ECI Mild comorbidity		.155	1.643	.828	3.260
ECI Moderate comorbidity		.002	3.658	1.585	8.440
ECI Severe comorbidity		.006	4.236	1.524	11.777

A model that included all variables was carried out and certain categories within the explanatory variables were shown to be significantly associated with outcome. As the Tayside data was nearly complete we looked closely at the prognostic effect of variables such HNC Type, stage, smoking and alcohol status had in this cohort. In this model, laryngeal cancer was noted to affect survival as it had a protective effect with a HR of 0.436 which was statistically significant with a p value of 0.007. In terms of smoking status only ex smokers had a 2 fold risk attenuation for suvival with HR of 2.316 p=0.017. For alcohol status only harmful drinking affected survival with HR of 1.499. This result was marginally statistically insignificant with p=0.051. When considering disease stage, Stage 1 disease had a survival effect as risk of death was 2 times higher than Stage 0)with HR=2.407, p=0.044. For comorbidity measured using ECI only mild comorbidity was shown to affect survival as it reached statistical significance with HR of 3.150 and p=0.002, demonstrating a 3 fold risk of death for patients with mild comorbidity levels in comparison to their counterparts without comorbidity.

The next step was to conduct the Cox regression using SIMD income and education quintiles as the measure of SES (Table 43). Laryngeal cancer continued to have better survival with HR=0.513

(p=0.026). In this model both moderate and heavy smokers had significant risk of death with HRs of 3.262 (p=0.039) and 3.642 (p=0.011) respectively. Education appeared to be closely linked to survival, in particular quintile 4 had a hazard of 3.667 with a significance level of p=0.026. Although quintile 5 (least educated) did not achieve statistical significance due to a high p value of 0.070, the HR of 3.292 is worth mentioning as it may be clinically relevant in predicting survival. From the results it would appear that survival worsened by educational attainment. Moderate comorbidity was shown to affect survival as there was a notable increase in the risk of death by up to 4 times with HR of 4.265 (p=0.001). Similarly severe comorbidity reduced survival even further as the risk of death increased to nearly 5 times with a hazard of 4.760 (p=0.003).

Table 43 Cox Model of ECI + SIMD Income and education + All variables

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Lowest Income quintile (Ref group)	4	.477			
Quintile 2		.413	.699	.296	1.649
Quintile 3		.252	.536	.184	1.560
Quintile 4		.257	.530	.176	1.590
Highest Income quintile		.068	.318	.093	1.087
Most educated quintile (Ref group)	4	.175			
Quintile 2		.765	1.148	.464	2.840
Quintile 3		.222	1.926	.673	5.508
Quintile 4		.026	3.667	1.169	11.506
Least educated quintile		.070	3.292	.906	11.964
ECI None (Ref group)	3	.001			
ECI Mild comorbidity		.102	1.773	.892	3.523
ECI Moderate comorbidity		.001	4.265	1.755	10.364
ECI Severe comorbidity		.003	4.760	1.712	13.236

As the patterns of survival associated with income did not demonstrate a clear linear relationship for poor survival by income levels, we decided to combine the previous model with CCI. In the results of that Cox regression analysis, we noted that the inclusion of age in this model appeared to distort the size of the effect as the HRs for CCI categories were 0.000 which may have been due to summary CCI scores having been calculated inclusive of age.

The next model we ran dropped the age variable as this was already incorporated in the calculation of the CCI scores and here again; we used both the CCI and ECI in the model to check

if there was an increase in the hazard ratios. The results of this analysis showed that laryngeal cancer was protective (HR=0.508 (p=0.023)). The other HNCs appeared to increase risk of death but those results did not reach statistical significance. Smoking status showed risk attenuation, especially for heavy smoking which reached statistical significance with HR of 3.123 (p=0.026). ECI measured comorbidity status was also linked to amplified risk with moderate comorbidity having HR=2.783 and p=0.021. Severe comorbidity had a HR of 3.343 and p of 0.024. Comorbidity measured using CCI did not show an effect as the parameter estimates did not achieve statistical significance and the 95%CI included 1.

In a model that substituted Scottish SIMD quintiles with SIMD income and education domain quintiles, we noted that there was modification of risk estimates. Although most variables did show an increase by each incremental level, the results did not achieve statistical significance therefore a clear influence on survival was unclear. A constant protective effect for laryngeal cancer similar to that from previous models was confirmed here with HR 0.563 and p=0.049. Smoking status, specifically heavy smoking was associated with reduced survival, with a hazard of 3.558 (p=0.014). Comorbidity was also linked to poor survival, with moderate comorbidity having a HR of 2.794 (p=0.028) and severe comorbidity HR= 3.150 (p=0.030).

We conducted another model where we analysed the influence of all predictors based on CCI.

Table 44 Cox Model of All variables ECI, CCI and SIMD income and education.

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Lowest Income quintile (Ref group)	4	.527			
Quintile 2		.958	.978	.428	2.234
Quintile 3		.310	.584	.207	1.648
Quintile 4		.198	.485	.161	1.459
Highest Income quintile		.112	.377	.113	1.256
Most educated quintile (Ref group)	4	.229			
Quintile 2		.936	1.038	.421	2.559
Quintile 3		.353	1.631	.580	4.585
Quintile 4		.044	3.283	1.033	10.436
Least educated quintile		.124	2.733	.760	9.832
CCI None/Mild (Ref group)	2	.121			
CCI Moderate		.356	.618	.222	1.718
CCI Severe		.899	1.070	.377	3.038
ECI None (Ref group)	3	.040			
ECI Mild comorbidity		.181	1.626	.798	3.314
ECI Moderate comorbidity		.028	2.794	1.116	6.998
ECI Severe comorbidity		.030	3.150	1.115	8.900

Since some of the variables used to conduct the analysis had missing values, particularly the SES indicators, the decision was reached to conduct multiple imputations in order to improve the methodological rigour and validity of these findings. The results of the imputation analysis are presented in the next section.

6.3.4. Results of Multiple Imputations in Tayside dataset

The first model fitted with the imputed data was that for CCI and the SIMD income and education domains. The model had issues of constant dependence which meant that the income and education quintiles could not be modelled as categorical variables. The imputed data showed better prediction than the original data with worse risk of death for increased comorbidity. A model using the Scottish SIMD data as the SES measure and CCI was conducted (Table 45). The model was able to show that chance of survival decreased with each incremental level of comorbidity, and similarly for SES, worsening survival was noted for the less affluent SIMD quintiles.

Table 45 Cox Model of CCI, SIMD Income and Education with MI data

Explanatory variables	SE	Sig	HR	95% CI for HR	
				Lower	Upper
CCI Moderate	.436	.555	1.293	.550	3.041
CCI Severe	.425	.019	2.702	1.174	6.219
Quintile 2	.257	.928	.977	.590	1.618
Quintile 3	.284	.618	.868	.495	1.521
Quintile 4	.236	.734	.923	.580	1.467
Least deprived SIMD quintile	.285	.673	.887	.507	1.551

The next step was to attempt to run a Cox model with all the key variables using SIMD income and education domains as the SES measure. Table 48 shows the results of that analysis. HNC type was included as a continuous variable as linear dependence posed problems in the model. Notably only heavy smoking appeared to be linked to premature mortality in the pooled analysis. The imputations did not add anything new to the analysis as evidenced by the change between standard errors in the original and pooled data.

Table 46 Cox Model of All variables, CCI+ SIMD Income and Education with MI data

Explanatory variables	SE	Sig	HR	95% CI for HR	
				Lower	Upper
CCI Mild	1.622	.231	.139	.005	3.680
CCI Moderate	1.624	.292	.177	.007	4.702
CCI Severe	1.610	.112	.074	.003	1.887
Education Quintiles	.128	.217	1.172	.909	1.511
Income Quintiles	.113	.782	.969	.775	1.211

In the analysis using ECI (Table 47) as the comorbidity measure, the hazards of death were more pronounced in this simple multivariate model which included Scottish SIMD quintiles and ECI only. The change in standard errors between the original and pooled data showed that the imputation did not fit the data well, therefore this model could not demonstrate survival influences of the prognostic factors.

Table 47 Cox Model of ECI and Scottish SIMD quintile with MI data

Explanatory variables	SE	Sig	HR	95% CI for HR	
				Lower	Upper
ECI Mild comorbidity	.245	.031	1.703	1.050	2.762
ECI Moderate comorbidity	.287	.001	2.678	1.505	4.766
ECI Severe comorbidity	.430	.685	1.192	.501	2.837
Quintile 2	.264	.842	1.054	.628	1.769
Quintile 3	.272	.415	.801	.469	1.367
Quintile 4	.238	.815	.946	.593	1.509
Least deprived SIMD quintile	.293	.957	.984	.554	1.749

The same issue that was highlighted for the Fife data where co-linearity caused issues with getting reliable risk estimates for income quintiles was noted in this analysis; therefore further models that were run did not treat income or HNC Type as categorical variables. Table 48 demonstrated a reduction in survival of up to 1.7 times (p=0.031) for mild comorbidity and nearly 2.7 times (p=0.001) for moderate comorbidity. The other variables did not show a statistically significant risk of death.

A proportional hazards model that used Scottish SIMD, ECI and the other key predictor variables showed the magnitude of the effect of adding in the imputed data. The analysis showed that most of the variables had a role in determining outcomes although it was less clear for Scottish SIMD (Table 48). Only moderate comorbidity was able to demonstrate risk of death with a hazard of 2.298 (p=0.006).

Table 48 Cox Model of all variables including Scottish SIMD quintiles and ECI with MI data

Explanatory variables	SE	Sig	HR	95% CI for HR	
				Lower	Upper
Quintile 2	.292	.662	1.137	.636	2.031
Quintile 3	.284	.700	.896	.513	1.565
Quintile 4	.244	.903	1.030	.638	1.664
Least deprived SIMD quintile	.314	.717	.892	.481	1.654
ECI Mild comorbidity	.258	.295	1.311	.787	2.185
ECI Moderate comorbidity	.296	.006	2.298	1.280	4.127
ECI Severe comorbidity	.425	.969	1.017	.435	2.375

An additional model that used all the same key variables and added in CCI as an additional comorbidity measure was run and the output is depicted in Table 49. As in previous models only moderate comorbidity in ECI showed an effect with HR=2.453 (p=0.002). Neither SIMD nor CCI were able to demonstrate an improvement in survival as their parameter estimates did not reach statistical significance and the 95% CIs included 1.

Table 49 Cox Model of All variables with MI data

Explanatory variables	SE	Sig	HR	95% CI for HR	
				Lower	Upper
Quintile 2	.274	.435	1.239	.723	2.124
Quintile 3	.312	.799	.924	.498	1.713
Quintile 4	.249	.974	.992	.608	1.617
Least deprived SIMD quintile	.310	.824	.933	.508	1.714
ECI Mild comorbidity	.266	.196	1.411	.836	2.383
ECI Moderate comorbidity	.288	.002	2.453	1.396	4.313
ECI Severe comorbidity	.479	.187	1.895	.728	4.936
CCI Mild	1.633	.275	.163	.006	4.568
CCI Moderate	1.640	.274	.161	.006	4.596
CCI Severe	1.598	.078	.056	.002	1.405

This combined model (shown in Table 50) did not improve the prediction of survival when compared to an earlier model that used only the ECI (Table 47). When Scottish SIMD was substituted with SIMD income and education quintiles the likelihood of worsening survival was increased (Table 50). Only ECI measured moderate comorbidity had a statistically significant effect on survival prospects with HR=2.530, p=0.001.

Table 50 Cox Model All variables, ECI, SIMD Income and Education with MI data

Explanatory variables	SE	Sig	HR	95% CI for HR	
				Lower	Upper
Income Quintiles	.123	.763	.964	.755	1.229
Education Quintiles	.135	.208	1.189	.906	1.560
CCI Mild	1.687	.255	.141	.005	4.408
CCI Moderate	1.712	.251	.134	.004	4.472
CCI Severe	1.662	.082	.051	.002	1.480
ECI Mild comorbidity	.276	.206	1.421	.823	2.454
ECI Moderate comorbidity	.277	.001	2.530	1.471	4.352
ECI Severe comorbidity	.504	.243	1.818	.655	5.051

6.4.1. Full cohort results

We conducted a cross tabulation based on both comorbidity and SES to investigate whether there was an age associated pattern to comorbidity and whether there was a social patterning to stage of disease at diagnosis. We began with CCI and age. This showed that older patients had more severe comorbidity levels (see Table 51)

Table 51 Cross tabulation of Age and CCI Full cohort

		CCI			Total
		None/Mild	Moderate	Severe	
Age Group	**<40 years**	17	0	0	17
	41-50 years	32	20	8	60
	51-60 years	22	111	81	214
	61-70 years	29	102	229	360
	71+ years	59	11	427	497
Total		159	244	745	1148

The same effect was apparent for age and ECI as depicted in Table 52.

Table 52 Cross tabulation of Age and ECI Full cohort

Age Group		ECI				Total
		None	**Mild**	**Moderate**	**Severe**	
	<40 years	16	1	0	0	17
	41-50 years	56	0	4	0	60
	51-60 years	169	16	24	5	214
	61-70 years	273	48	33	6	360
	71+ years	341	83	66	8	498
Total		855	148	127	19	1149

The influence of SES on disease stage was explored next using first Scottish SIMD quintiles which showed that more advanced disease occurred in patients from the most deprived quintiles as shown in Table 53. Across all quintiles, more patients presented with advanced disease and these results were similar for income and education domains, (See Tables 54 and 55).

Table 53 Cross tabulation of Disease Stage and Scottish SIMD quintiles Full cohort

		Scottish SIMD quintiles					Total
		1	**2**	**3**	**4**	**5**	
Stage	**Stage 0**	7	11	9	8	9	44
	Stage I	30	52	31	36	25	174
	Stage II	35	27	23	25	16	126
	Stage III	44	28	29	22	13	136
	Stage IV	92	73	70	70	43	348
Total		208	191	162	161	106	828

Table 54 Cross tabulations of Disease stage and Income quintiles Full cohort

		Scottish SIMD quintiles					Total
		1	**2**	**3**	**4**	**5**	
Stage	**Stage 0**	7	12	6	6	14	45
	Stage I	28	32	29	55	36	180
	Stage II	20	18	22	36	32	128
	Stage III	12	29	22	28	45	136
	Stage IV	44	62	63	81	101	351
Total		111	153	142	206	228	840

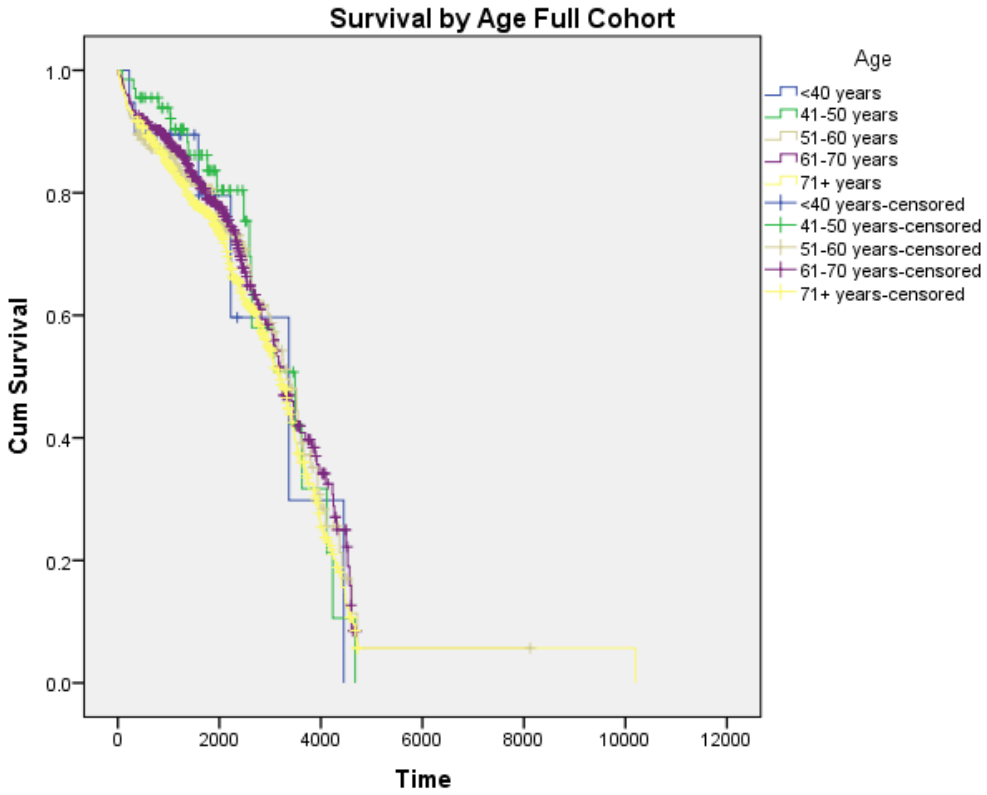
Table 55 Cross tabulations of Disease stage and Education quintiles Full cohort

		Scottish SIMD quintiles					Total
		1	**2**	**3**	**4**	**5**	
Stage	**Stage 0**	7	8	11	10	9	45
	Stage I	29	28	37	49	37	180
	Stage II	15	21	25	26	41	128
	Stage III	16	21	29	31	39	136
	Stage IV	46	67	55	92	91	351
Total		113	145	157	208	217	840

6.4.2. Results of Kaplan-Meier Analysis in Full cohort dataset

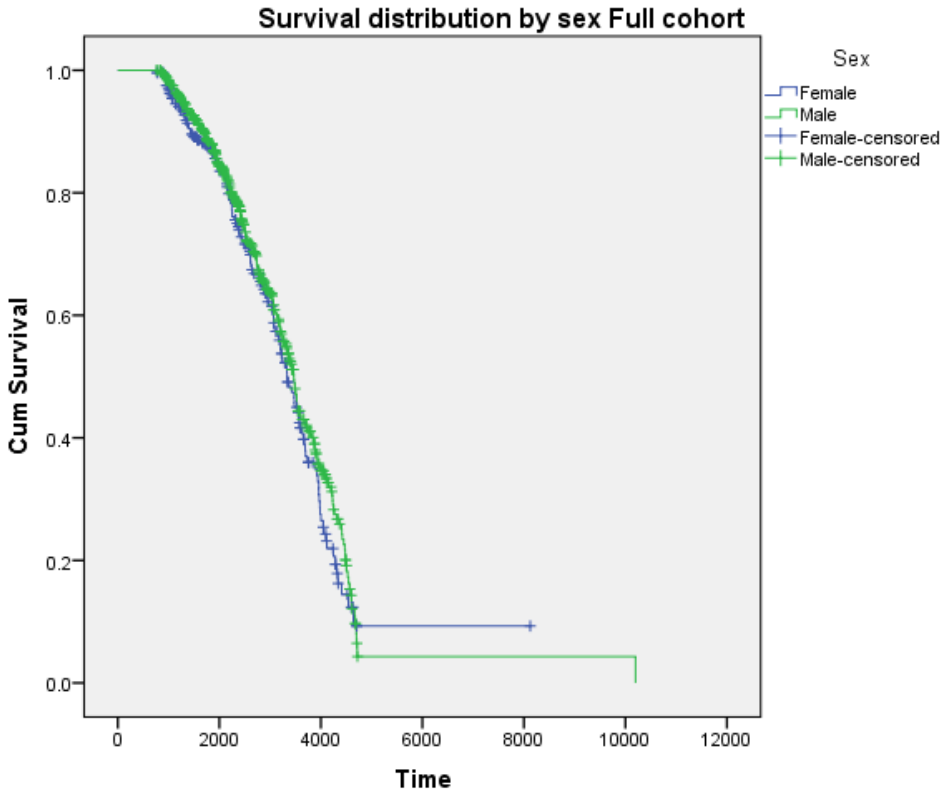
The probability of surviving dependent on age was examined and older patients had higher risk of poorer survival compared to their younger counterparts as depicted in Figure 39. The majority of the patients died within the first five years and older patients aged 41 -50 years appeared to have the worst survival which did not match up with the expected age related gradient in survival. The result was not statistically significant with evidence of differences between age groups defined by X^2 =3.439 (p=0.487).

Figure 39 Survival distributions by Age group in Full cohort



When considering survival based on gender (Figure 40), the log rank test did not find any significant differences between the two groups, $X^2 = 152.567$ ($p<0.0001$) although the survival curve appeared to indicate that being female was linked to better survival. These findings should be treated with some caution as there were two missing cases within the analysis.

Figure 40 Survival by Gender in Full cohort



There were 126 female deaths compared to 236 in males over the same time period, but as the male to female ratio was approximately 2:1 these findings are not surprising. In terms of sex, the log rank test did not find statistically significant differences in survival, with X^2= 1.129 (p=0.288). In terms of HNC type, the log rank test for survival reached statistical significance with X^2= 32.479 (p<0.0001).

Figure 41 Survival by HNC type in Full cohort

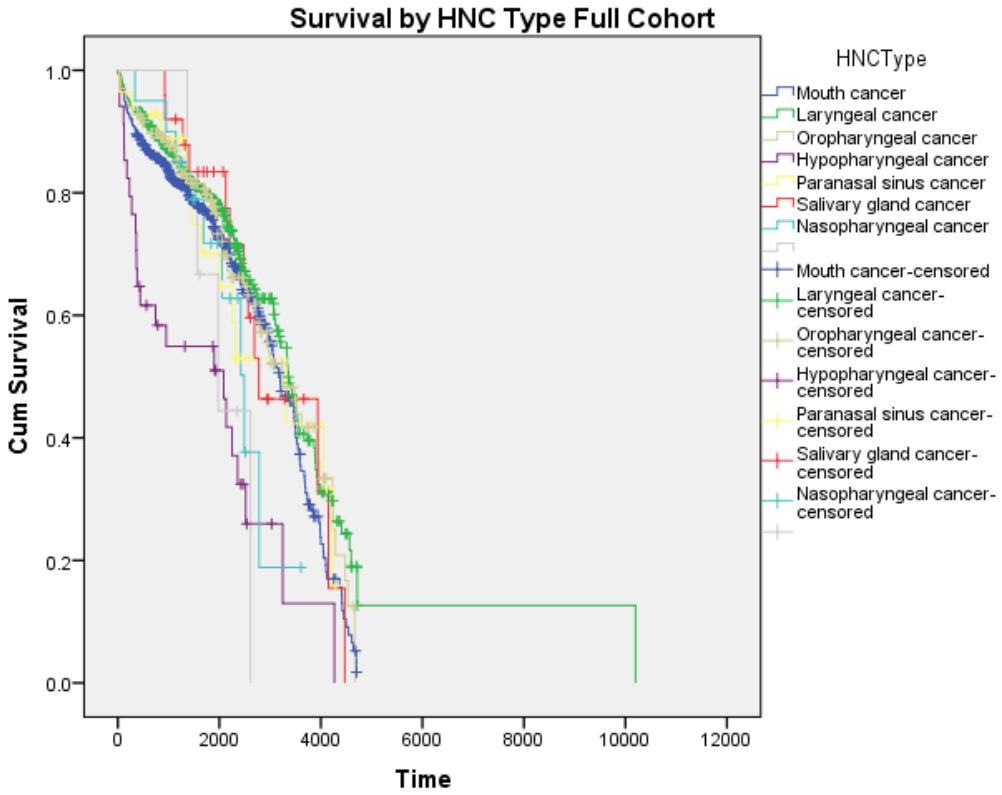
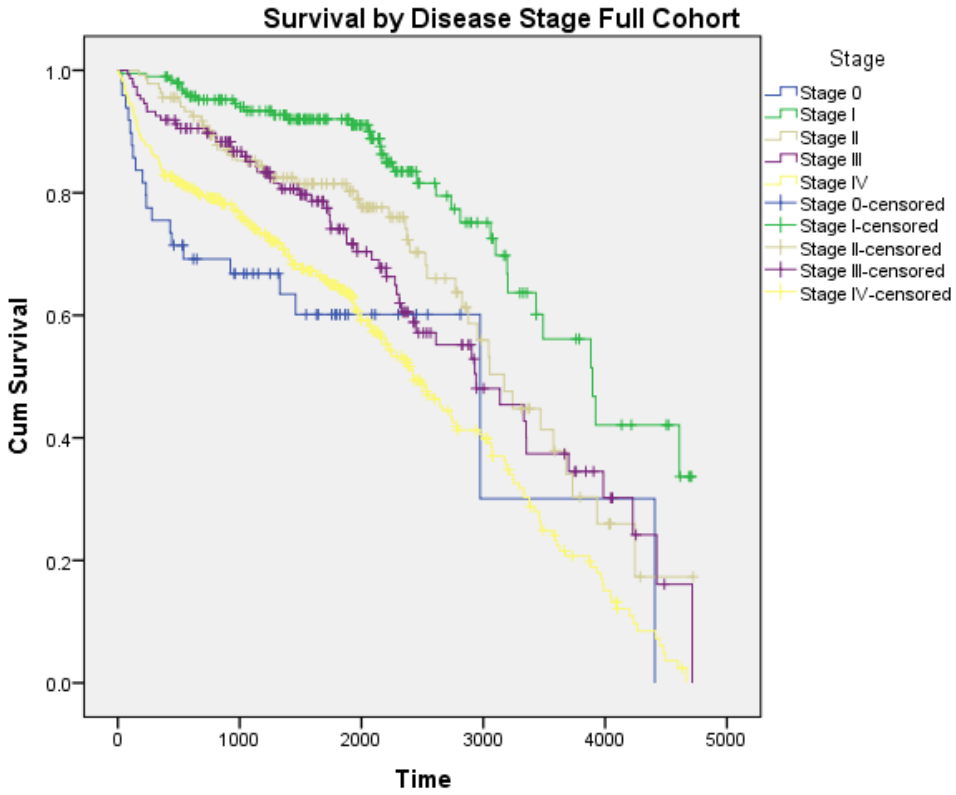


Figure 41 shows that laryngeal cancers had better mean survival times (3776.62) which were better than those for hypopharyngeal cancer which had median survival times of 1769.201. Survival distributions by disease stage appeared to follow the expected pattern of worse outcomes for advanced disease, as Stage 0 had better survival (Figure 42).

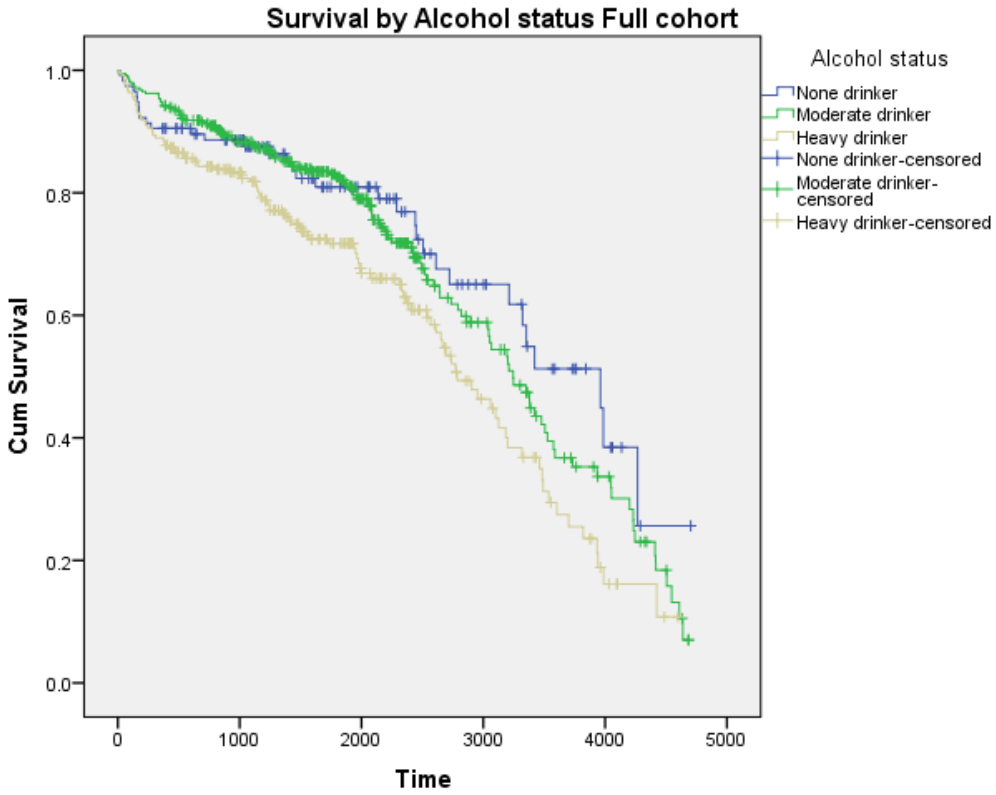
Figure 42 Survival distributions by Disease stage in Full cohort



The log rank test for disease stage had evidence of statistically significant differences between the groups with X^2 of 66.713 and p<0.0001 (Figure 42).

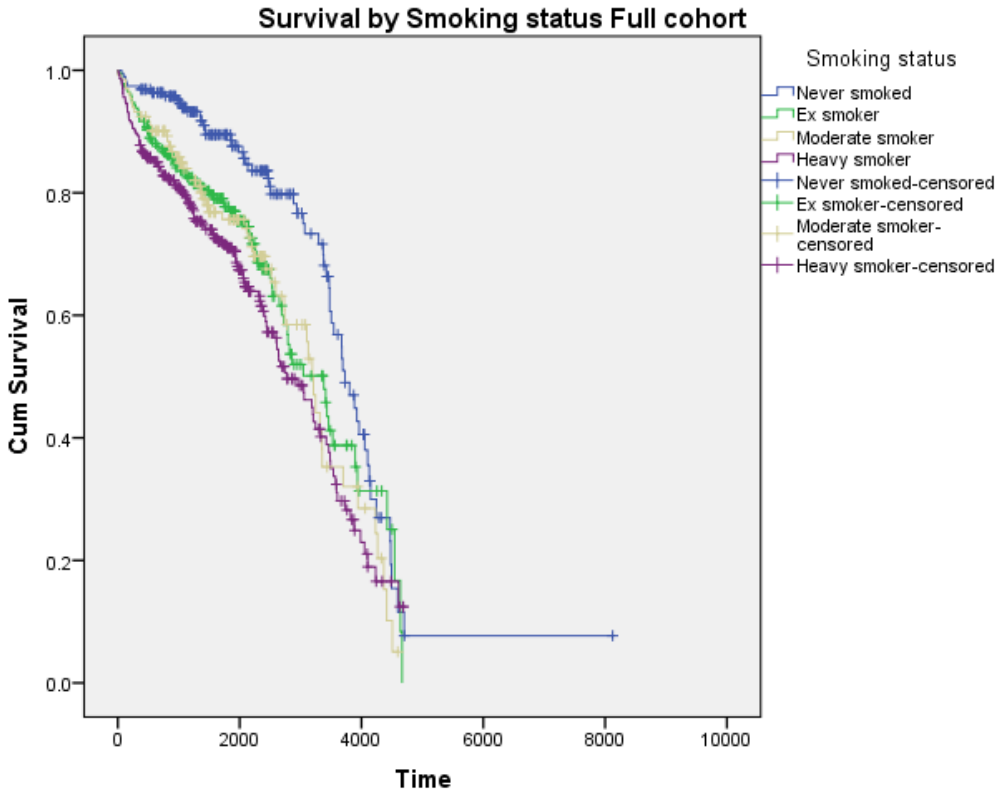
In terms of alcohol status we found this variable reached statistical significance, X^2= 11.168, p=0.004 (Figure 43), with none drinkers appearing to have better survival compared to the other groups.

Figure 43 Survival distributions by Alcohol status in Full cohort



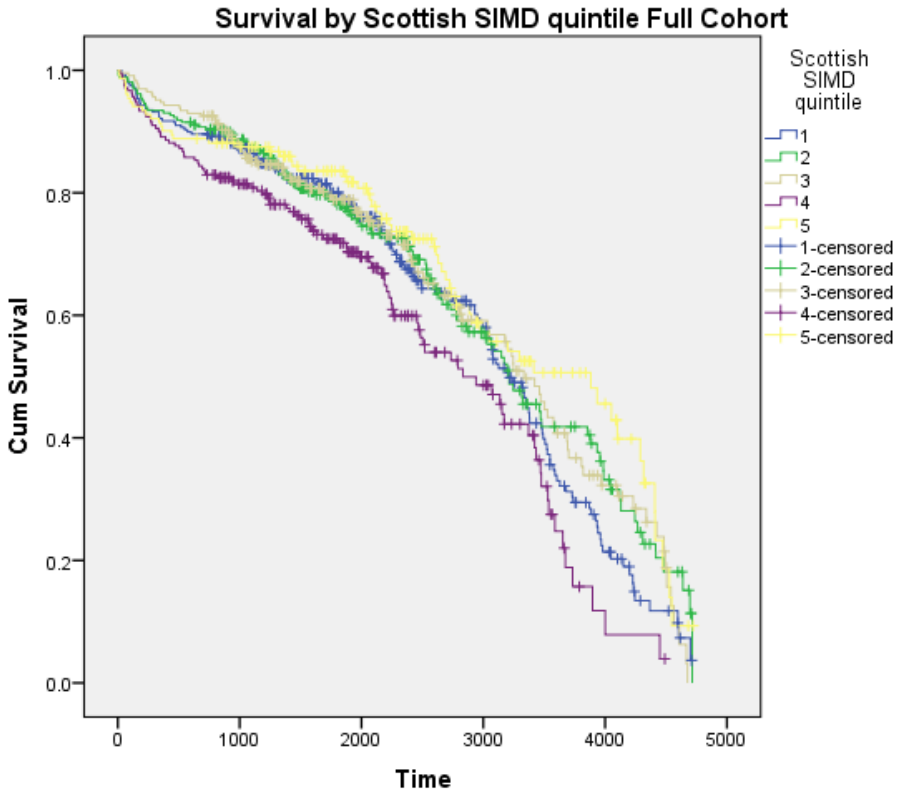
On considering smoking status, (Figure 44) we found that non-smokers had the superior outcomes compared to the other smoking groups. This survival distribution followed a gradient with heavy smokers having the poorest survival. This relationship was highly statistically significant with X^2 test result of 20.848 ($p<0.0001$). Mean survival time comparisons between non-smokers and heavy smokers were 3748.161 and 2669.042 respectively. The mean survival time for heavy smoking group was significantly less than the overall survival time of 3143.295.

Figure 44 Survival distributions by Smoking status in Full cohort



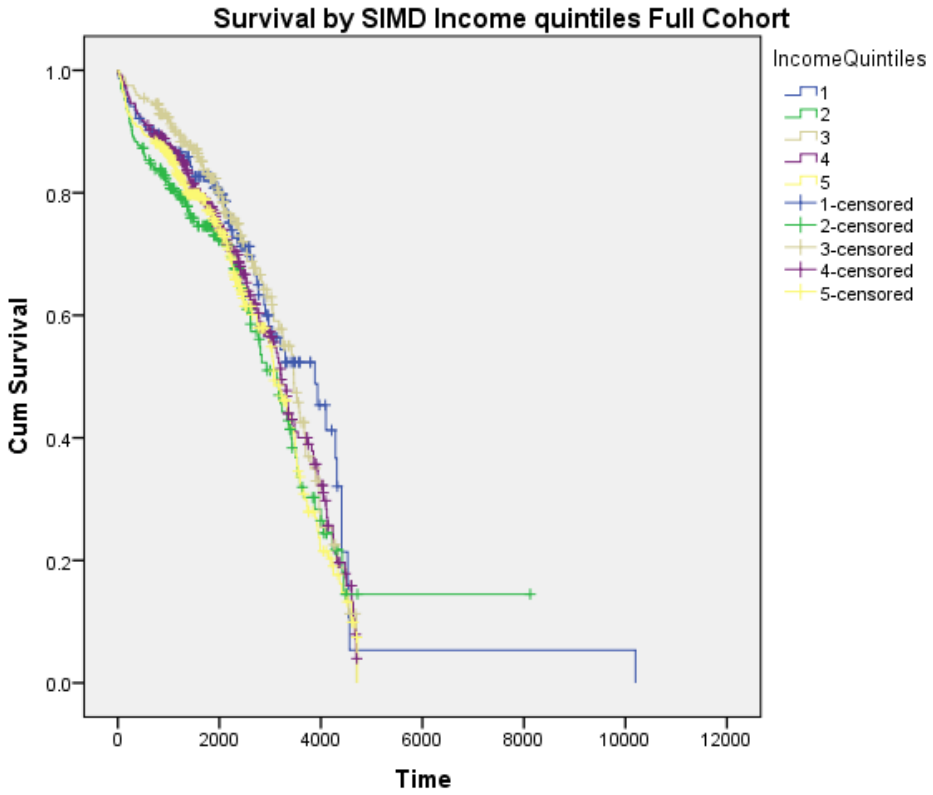
Survival estimates were conducted based on SES (Figure 45) at first using Scottish SIMD quintiles. It was apparent that an inverse relationship existed with lowest quintile patients having worse survival. The log rank test had evidence of statistically significant differences between groups. It was apparent that patients from quintile 4 had worse chances of survival compared to their counterparts with X^2 = 15.172 (p=0.004). Quintile 5 had better survival, (mean survival time of 3179.25 compared to 2947.443 for overall survival time).

Figure 45 Survival distributions by Scottish SIMD quintile in Full cohort



Due to the unexpected finding of the Scottish SIMD quintiles analysis, we conducted an analysis of the survival distribution using the income and education quintiles.

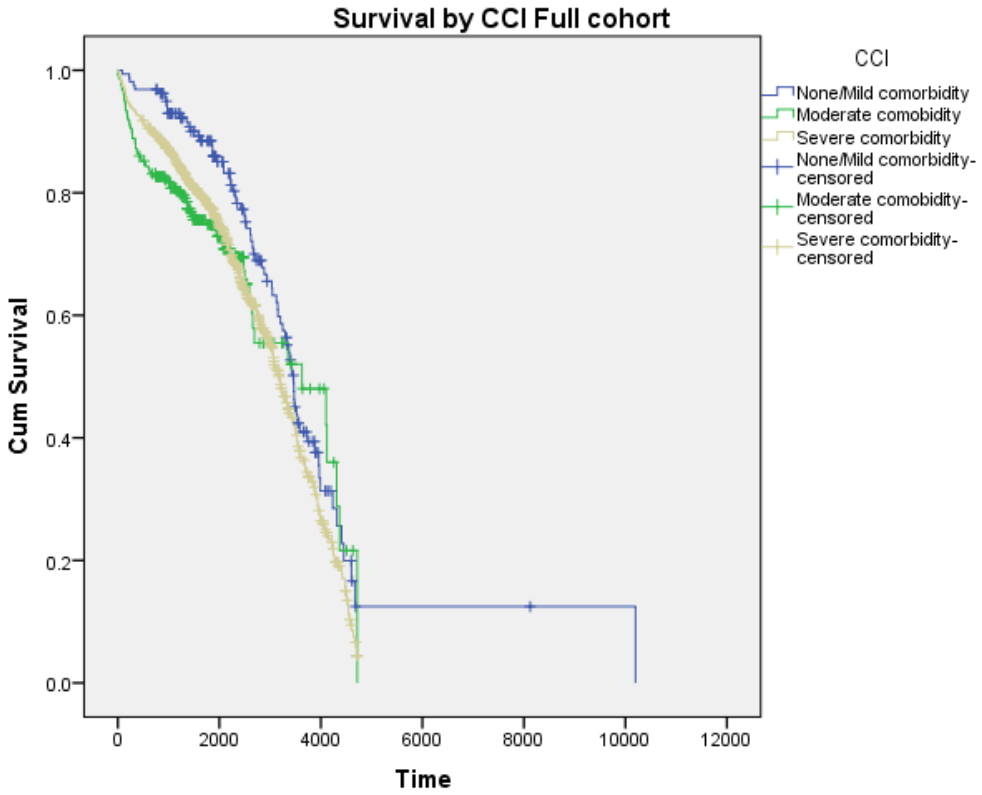
Figure 46 Survival distributions by SIMD Income quintiles in Full cohort



The analysis of income quintiles (Figure 46) showed that the least deprived quintile had the worst outcomes, however this result did not reach statistical significance with X^2 of 6.452 (p=0.168). SIMD education quintiles were not shown to be statistically significant (X^2=3.053, p=0.549) and survival distribution between quintiles did not follow a predetermined relationship of worse survival in the most deprived.

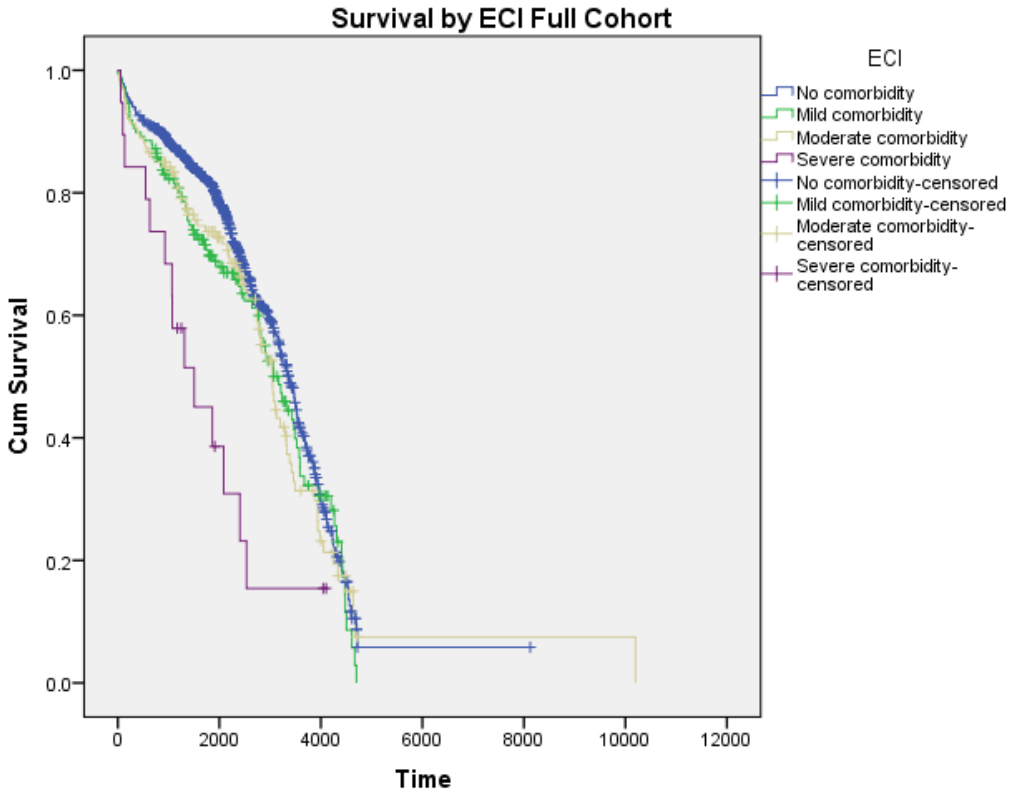
The survival distribution for comorbidity was the next variable to be assessed. The analysis using CCI (Figure 47) showed that the dichotomised none/mild comorbidity category had the better survival with mean survival time of 3957.734 days compared to 2918.699 days for severe comorbidity. This result was statistically significant p=0.047 and X^2=6.135.

Figure 47 Survival distributions by CCI in Full cohort



When comorbidity using ECI was used to estimate survival, severe comorbidity was shown to be linked to poor survival (Figure 48). The log rank test statistic had statistical significance with X^2 score of 16.559 (p=0.001) showing that there were differences in the survival distribution of ECI.

Figure 48 Survival distributions by ECI in Full cohort



6.4.3. Cox proportional hazards regression analysis – Full Cohort

As the independent analysis showed that most of the factors had some prognostic importance, Cox regression modelling was applied in order to find out which categories within the explanatory (predictor) variables had the ability to predict survival. Survival analysis of the cohort was conducted to estimate the prognostic impact of comorbidity and SES on time to the event of interest (death) of an individual.

The outcomes for the individual Cox proportional hazards regression analysis for the predictor variables are shown in Tables 55 to 60.

Table 56 Initial Cox Model of CCI and Scottish SIMD quintiles Full cohort

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
CCI None (Ref group)	3	.068			
CCI Mild		.101	1.319	.948	1.836
CCI Moderate		.011	1.430	1.086	1.883
CCI Severe		.188	1.204	.913	1.588
Most deprived SIMD quintile (Ref group)	4	.005			
Quintile 2		.201	.849	.661	1.091
Quintile 3		.329	.880	.680	1.138
Quintile 4		.044	1.311	1.007	1.706
Least deprived SIMD quintile		.062	.750	.555	1.014

In Table 56, CCI did not display a consistent prognostic influence on survival although moderate comorbidity had a hazard of 1.43 which was significant with p=0.011. Scottish SIMD quintiles had similar results with only Quintile 4 achieving statistical significance with p=0.044 and hazard of death of 1.311. A subsequent model that used SIMD income and education domains in the place of the Scottish SIMD quintiles (Table 58) found that the two measures of SES although possessing hazard ratios that were greater than 1, the results were not statistically significant as they were greater than the p<0.05. The mild and moderate categories of CCI were noted to have reached statistical significance with HRs of 1.409 (p=0.042) and 1.509(p=0.004) respectively.

Table 57 Cox Model of SIMD Income and Education Full cohort

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Lowest Income quintile (Ref group)	4	.266			
Quintile 2		.119	1.319	.931	1.869
Quintile 3		.912	1.026	.656	1.602
Quintile 4		.427	1.218	.749	1.980
Highest t Income quintile		.251	1.359	.805	2.293
Most educated quintile (Ref group)	4	.693			
Quintile 2		.194	1.258	.890	1.780
Quintile 3		.856	1.040	.681	1.589
Quintile 4		.756	1.079	.667	1.747
Least educated quintile		.882	1.040	.619	1.748
CCI None (Ref group)	3	.030			
CCI Mild		.097	1.267	.958	1.675
CCI Moderate		.042	1.409	1.012	1.961
CCI Severe		.004	1.506	1.141	1.987

In Table 57, patients with oropharyngeal cancer were shown to have significantly better overall survival (HR=0.630, p=0.030). Smoking status showed that being a heavy smoker appeared to be associated with poor survival, with the risk of death to 4.263 p<0.0001. The two prognostic factors SES and comorbidity did not illustrate an effect on survival.

Table 58 Cox Model of All variables, CCI + SIMD quintiles Full cohort

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Mouth cancer (Ref group)	6	.230			
Laryngeal cancer		.132	.766	.541	1.084
Oropharyngeal cancer		.030	.630	.415	.956
Hypopharyngeal cancer		.740	.901	.486	1.669
Paranasal sinus cancer		.709	1.222	.426	3.502
Nasopharyngeal cancer		.464	.469	.062	3.553
Salivary gland cancer		.467	1.377	.582	3.257
None smoker (Ref group)	3	.000			
Ex smoker		.072	1.506	.964	2.350
Moderate smoker		.464	1.163	.776	1.742
Heavy smoker		.000	4.263	2.556	7.109
Non-drinker (Ref group)	2	.147			
Moderate drinker		.856	1.038	.693	1.554
Harmful drinker		.097	1.387	.942	2.041
Stage 0 (Ref group)	4	.000			
Stage 1		.144	.445	.150	1.318
Stage 2		.723	.825	.286	2.384
Stage 3		.904	.936	.320	2.733
Stage 4		.347	1.637	.586	4.576
Most deprived SIMD quintile (Ref group)	4	.599			
Quintile 2		.769	.942	.635	1.400
Quintile 3		.863	1.040	.668	1.617
Quintile 4		.172	1.343	.880	2.050
Least deprived SIMD quintile		.927	.977	.589	1.620
CCI None (Ref group)	3	.025			
CCI Mild		.381	.753	.400	1.420
CCI Moderate		.367	1.297	.737	2.282
CCI Severe		.184	1.488	.828	2.676
Female (Ref group)	1	.251			
Male		.116	.186	.023	1.518

Another model was run comparing HNC types to mouth cancer and appeared to show that hypopharyngeal cancers had the worst survival HR=2.037, and this result reached statistical significance, p=0.018. Laryngeal cancer had the best survival estimates compared to mouth

cancer with HR=0.648 (p=0.015). There was evidence of an attenuation of risk in correspondence to the increase of smoking habits, with heavy smokers having up to 2 times an increased risk of death compared to ex-smokers who had 1.5 times the risk of death (Table 59).

Table 59 Cox Model of HNC Type, smoking and alcohol status, Scottish SIMD and CCI

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Mouth cancer (Ref group)	6	.011			
Laryngeal cancer		.015	.648	.456	.919
Oropharyngeal cancer		.972	.993	.665	1.483
Hypopharyngeal cancer		.018	2.037	1.127	3.681
Paranasal sinus cancer		.382	.662	.263	1.669
Nasopharyngeal cancer		.790	.892	.384	2.071
Salivary gland cancer		.151	1.857	.798	4.324
None smoker (Ref group)	3	.045			
Ex smoker		.088	1.587	.934	2.696
Moderate smoker		.046	1.759	1.010	3.064
Heavy smoker		.006	2.041	1.231	3.383
Non-drinker (Ref group)	2	.027			
Moderate drinker		.208	1.353	.845	2.166
Harmful drinker		.015	1.833	1.126	2.983
Most deprived SIMD quintile (Ref group)	4	.242			
Quintile 2		.079	.702	.473	1.042
Quintile 3		.098	.698	.456	1.069
Quintile 4		.894	1.029	.672	1.576
Least deprived SIMD quintile		.445	.834	.523	1.329
CCI None/Mild (Ref group)	2	.419			
CCI Moderate		.481	1.223	.698	2.142
CCI Severe		.210	1.366	.838	2.227

After replacing Scottish SIMD quintiles with SIMD income and education quintiles, (Table 60) the protective effect of oropharyngeal cancer remained significant. There was an improvement in prognosis with risk of death in heavy smokers to 3.605 with p<0.0001.

Table 60 Cox Model All variables, CCI + SIMD Income and Education Full cohort

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Mouth cancer (Ref group)	6	.214			
Laryngeal cancer		.391	.858	.606	1.216
Oropharyngeal cancer		.034	.634	.416	.965
Hypopharyngeal cancer		.871	1.051	.575	1.922
Paranasal sinus cancer		.654	1.273	.444	3.653
Nasopharyngeal cancer		.318	.356	.047	2.697
Salivary gland cancer		.401	1.450	.609	3.454
None smoker (Ref group)	3	.000			
Ex smoker		.126	1.407	.909	2.179
Moderate smoker		.636	1.105	.730	1.675
Heavy smoker		.000	3.605	2.235	5.815
Non-drinker (Ref group)	2	.335			
Moderate drinker		.971	1.007	.677	1.500
Harmful drinker		.237	1.266	.856	1.871
Stage 0 (Ref group)	4	.000			
Stage 1		.107	.409	.138	1.214
Stage 2		.736	.833	.289	2.404
Stage 3		.763	.848	.290	2.476
Stage 4		.393	1.568	.558	4.405
Lowest Income quintile (Ref group)	4	.730			
Quintile 2		.789	.922	.508	1.672
Quintile 3		.261	.660	.320	1.363
Quintile 4		.679	.856	.411	1.785
Highest Income quintile		.678	.843	.377	1.886
Most educated quintile (Ref group)	4	.344			
Quintile 2		.265	1.394	.777	2.500
Quintile 3		.714	1.134	.580	2.216
Quintile 4		.231	1.550	.756	3.177
Least educated quintile		.818	1.098	.494	2.443
Female (Ref group)	1	.218			
Male		.136	.205	.026	1.643

After replacing CCI with ECI and retaining Scottish SIMD quintiles (Table 61), the Cox proportional hazards regression showed an reduction in survival for SIMD quintile 4, HR=1.347 (p=0.026).

Severe comorbidity also had poor survival prospects with HR of 2.689 p<0.0001.

Table 61 Cox Model of Scottish SIMD and ECI Full cohort

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Most deprived SIMD quintile (Ref group)	4	.004			
Quintile 2		.217	.854	.666	1.097
Quintile 3		.468	.909	.703	1.176
Quintile 4		.026	1.347	1.036	1.753
Least deprived SIMD quintile		.094	.773	.571	1.045
ECI None (Ref group)	3	.001			
ECI Mild comorbidity		.109	1.220	.957	1.555
ECI Moderate comorbidity		.073	1.258	.979	1.616
ECI Severe comorbidity		.000	2.689	1.568	4.612

After changing the Scottish SIMD quintiles and adding in SIMD income and education quintiles (Table 62), the statistical significance of the model was reduced. Only severe comorbidity reached statistical significance p<0.0001 with HR= 2.677 emphasising the poor survival prospects.

Table 62 Cox Model of ECI +SIMD Income and education quintiles Full cohort

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Lowest Income quintile (Ref group)	4	.327			
Quintile 2		.142	1.297	.917	1.834
Quintile 3		.872	1.038	.662	1.627
Quintile 4		.490	1.188	.728	1.939
Highest Income quintile		.265	1.350	.797	2.287
Most educated quintile (Ref group)	4	.724			
Quintile 2		.196	1.256	.889	1.773
Quintile 3		.778	1.063	.693	1.631
Quintile 4		.863	1.044	.642	1.697
Least educated quintile		.849	1.052	.623	1.776
ECI None (Ref group)	3	.001			
ECI Mild comorbidity		.066	1.260	.985	1.613
ECI Moderate comorbidity		.157	1.199	.933	1.542
ECI Severe comorbidity		.000	2.677	1.562	4.588

In the analysis presented in Table 63, we found that most of the variables were not significant with p>0.05. However both age and oropharyngeal cancers were noted to have protective effects on survival. Ex- smokers and heavy smokers were at high risk of poor survival with hazards of 1.667 (p=0.026) and HR= 4.229 (p<0.0001) respectively. Only moderate comorbidity was also shown to affect survival with HR=1.569 p=0.049.

Table 63 Cox Model All Variables, ECI and Scottish SIMD quintiles Full cohort

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
None smoker (Ref group)	3	.084			
Ex smoker		.028	1.916	1.071	3.427
Moderate smoker		.020	2.059	1.122	3.778
Heavy smoker		.016	1.986	1.135	3.477
Non-drinker (Ref group)	2	.240			
Moderate drinker		.274	1.348	.789	2.302
Harmful drinker		.099	1.583	.917	2.732
Stage 0 (Ref group)	4	.000			
Stage 1		.063	.303	.086	1.066
Stage 2		.503	.659	.195	2.233
Stage 3		.740	.814	.240	2.756
Stage 4		.673	1.291	.394	4.227
Most educated quintile (Ref group)	4	.337			
Quintile 2		.367	1.335	.713	2.499
Quintile 3		.980	1.010	.478	2.132
Quintile 4		.302	1.530	.683	3.427
Least educated quintile		.158	1.882	.782	4.533
ECI None (Ref group)	3	.138			
ECI Mild comorbidity		.439	1.185	.771	1.822
ECI Moderate comorbidity		.049	1.569	1.002	2.457
ECI Severe comorbidity		.143	1.846	.812	4.197
Lowest Income quintile (Ref group)	4	.785			
Quintile 2		.753	.902	.476	1.711
Quintile 3		.516	.768	.345	1.706
Quintile 4		.563	.784	.344	1.789
Highest Income quintile		.279	.612	.251	1.490

In Table 63, age remained protective, while smoking status contributed to a reduction in survival in these patients. Ex smokers had HR=1.916 (p=0.028), moderate smokers, HR=2.059 (p=0.020) heavy smokers had HR= 1.459 (p=0.016). There was a stepwise linear gradient in survival for patients based on ECI comorbidity level, rising from hazards of 1.185 to as much as 1.846 although the results did not achieve statistical significance. As previous analyses had shown dependency between HNC type and Stage, we decided to remove stage from the model to see if there was any change in the hazard ratios. The results are shown in Table 64.

Table 64 Cox Model with key variables except Stage Full cohort

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Mouth cancer (Ref group)	6	.036			
Laryngeal cancer		.024	.667	.469	.948
Oropharyngeal cancer		.618	.901	.598	1.358
Hypopharyngeal cancer		.033	1.914	1.053	3.480
Paranasal sinus cancer		.483	.718	.285	1.811
Nasopharyngeal cancer		.811	.901	.384	2.115
Salivary gland cancer		.286	1.588	.679	3.711
None smoker (Ref group)	3	.044			
Ex smoker		.057	1.677	.984	2.857
Moderate smoker		.030	1.865	1.062	3.275
Heavy smoker		.005	2.086	1.249	3.482
Non-drinker (Ref group)	2	.036			
Moderate drinker		.105	1.487	.921	2.402
Harmful drinker		.013	1.878	1.145	3.080
Most educated quintile (Ref group)	4	.356			
Quintile 2		.158	1.546	.844	2.830
Quintile 3		.647	1.176	.587	2.355
Quintile 4		.159	1.755	.803	3.835
Least educated quintile		.153	1.846	.796	4.278
ECI None (Ref group)	3	.120			
ECI Mild comorbidity		.247	1.260	.852	1.865
ECI Moderate comorbidity		.335	1.216	.817	1.812
ECI Severe comorbidity		.031	2.258	1.075	4.740
Lowest Income quintile (Ref group)	4	.700			
Quintile 2		.847	1.061	.581	1.939
Quintile 3		.686	.853	.396	1.838
Quintile 4		.339	.676	.303	1.510
Highest Income quintile		.574	.783	.334	1.837

The exclusion of Stage showed an increase in survival estimates but the two SES predictors were not significant. In terms of comorbidity, only severe comorbidity was linked to outcome with a hazard of 2.258 (p=0.031).

Table 65 Cox Model of All variables + ECI and Scottish SIMD quintiles Full cohort

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Mouth cancer (Ref group)	6	.108			
Laryngeal cancer		.067	.719	.504	1.024
Oropharyngeal cancer		.060	.668	.438	1.018
Hypopharyngeal cancer		.962	1.015	.549	1.876
Paranasal sinus cancer		.513	1.424	.494	4.106
Nasopharyngeal cancer		.304	.347	.046	2.613
Salivary gland cancer		.818	1.109	.457	2.691
<40yrs (Ref group)	4	.000			
41-50yrs		.009	.193	.056	.662
51-60yrs		.002	.182	.062	.537
61-70yrs		.002	.177	.061	.516
71+ yrs		.053	.354	.124	1.014
None smoker (Ref group)	3	.000			
Ex smoker		.000	2.441	1.742	3.419
Moderate smoker		.016	1.459	1.073	1.984
Heavy smoker		.000	1.729	1.278	2.341
Non-drinker (Ref group)	2	.132			
Moderate drinker		.126	1.244	.940	1.644
Harmful drinker		.307	1.147	.881	1.493
Stage 0 (Ref group)	4	.000			
Stage 1		.116	1.735	.874	3.448
Stage 2		.057	1.788	.982	3.254
Stage 3		.237	.743	.455	1.215
Stage 4		.102	1.401	.936	2.098
Most deprived SIMD quintile (Ref group)	4	.767			
Quintile 2		.949	.987	.661	1.474
Quintile 3		.978	.994	.639	1.545
Quintile 4		.486	1.165	.758	1.789
Least deprived SIMD quintile		.390	.799	.478	1.334
Female (Ref group)	1	.089			
Male		.060	.136	.017	1.084
ECI None (Ref group)	3	.038			
ECI Mild comorbidity		.093	1.611	.924	2.808
ECI Moderate comorbidity		.815	.943	.580	1.535
ECI Severe comorbidity		.364	.828	.551	1.244

In the model presented in Table 65, ex-smokers had reduced survival with HR=2.441 ($p<0.0001$), as did moderate smoking which had a hazard of 1.459 ($p=0.016$), while heavy smokers had nearly a 2-fold risk of death with HR=1.729 which was a highly significant evidence of poor survival with $p<0.0001$. Neither comorbidity nor SES was able to give evidence of an effect on survival in this model.

Table 66 Cox Model of All variables ECI+ SIMD Income and education Full cohort

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Mouth cancer (Ref group)	6	.168			
Laryngeal cancer		.192	.790	.554	1.126
Oropharyngeal cancer		.077	.680	.443	1.043
Hypopharyngeal cancer		.971	.988	.532	1.838
Paranasal sinus cancer		.347	1.664	.576	4.804
Nasopharyngeal cancer		.264	.314	.041	2.398
Salivary gland cancer		.837	1.100	.444	2.725
None smoker (Ref group)	3	.000			
Ex smoker		.036	1.625	1.032	2.558
Moderate smoker		.496	1.160	.756	1.781
Heavy smoker		.000	4.546	2.754	7.503
Non-drinker (Ref group)	2	.271			
Moderate drinker		.970	1.008	.670	1.516
Harmful drinker		.205	1.297	.867	1.940
Stage 0 (Ref group)	4	.000			
Stage 1		.151	.448	.149	1.342
Stage 2		.867	.913	.314	2.653
Stage 3		.952	.967	.328	2.856
Stage 4		.309	1.718	.606	4.868
Lowest Income quintile (Ref group)	4	.885			
Quintile 2		.620	.857	.467	1.575
Quintile 3		.318	.686	.327	1.437
Quintile 4		.479	.758	.353	1.630
Highest Income quintile		.387	.691	.299	1.595
Most educated quintile (Ref group)	4	.304			
Quintile 2		.358	1.327	.726	2.427
Quintile 3		.504	1.264	.636	2.509
Quintile 4		.094	1.882	.897	3.948
Least educated quintile		.445	1.386	.600	3.201
ECI None (Ref group)	3	.018			
ECI Mild comorbidity		.617	1.113	.733	1.690
ECI Moderate comorbidity		.004	1.880	1.229	2.875
ECI Severe comorbidity		.135	1.859	.825	4.190

The analysis of survival concluded with a Cox model of all predictor variables and comorbidity measured by ECI, CCI and SES using Scottish SIMD income and education quintiles. The results are shown in Table 66 above. The same results were found with protective effects noted for laryngeal and oropharyngeal cancers as well as all age groups. A slight increase in survival estimates was noted for the variables with statistically significant categories. The risk for ex-smokers increased to HR=1.625 p=0.036 and for heavy smokers the hazard went up to HR=4.546,

p<0.0001. In terms of comorbidity only moderate comorbidity had a statistically significant effect on survival with a hazard of 1.880 p=0.004.

Table 67 Cox Model of All variables ECI, CCI +Scottish SIMD quintiles Full cohort

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
Mouth cancer (Ref group)	6	.121			
Laryngeal cancer		.048	.697	.487	.996
Oropharyngeal cancer		.046	.649	.424	.993
Hypopharyngeal cancer		.833	.935	.502	1.742
Paranasal sinus cancer		.466	1.481	.515	4.261
Nasopharyngeal cancer		.451	.454	.058	3.536
Salivary gland cancer		.808	1.116	.460	2.710
None smoker (Ref group)	3	.000			
Ex smoker		.040	1.607	1.021	2.531
Moderate smoker		.475	1.165	.767	1.769
Heavy smoker		.000	4.147	2.443	7.038
Non-drinker (Ref group)	2	.094			
Moderate drinker		.999	1.000	.663	1.508
Harmful drinker		.089	1.413	.949	2.104
Stage 0 (Ref group)	4	.000			
Stage 1		.176	.469	.157	1.403
Stage 2		.778	.858	.295	2.493
Stage 3		.975	.983	.333	2.896
Stage 4		.287	1.759	.622	4.972
Most deprived SIMD quintile (Ref group)	4	.811			
Quintile 2		.817	1.049	.699	1.575
Quintile 3		.856	1.042	.668	1.625
Quintile 4		.425	1.193	.774	1.838
Least deprived SIMD quintile		.533	.845	.498	1.435
CCI None (Ref group)		.313			
CCI Mild		.533	1.263	.607	2.630
CCI Moderate		.133	1.669	.856	3.255
CCI Severe		.367	1.401	.673	2.916
ECI None (Ref group)		.072			
ECI Mild comorbidity		.622	1.120	.714	1.756
ECI Moderate comorbidity		.011	1.778	1.139	2.774
ECI Severe comorbidity		.235	1.688	.712	4.004

As a comparator the analysis using CCI and ECI to classify comorbidity, was modified to include SIMD income and education quintiles for SES and all the other explanatory variables. The results are presented in the Table 67. ECI measured comorbidity demonstrated lower survival for patients with moderate comorbidity HR=1.778 (p=0.011). The results shown in Table 68 depict the

analysis for all the selected predictor variables when placed together in the multivariate proportional hazards regression analysis. Again moderate comorbidity is associated with poor survival with HR=1.886 (p=0.006).

Table 68 Cox Model of All variables, ECI, CCI + SIMD Income and education Full cohort

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
None smoker (Ref group)	3	.000			
Ex smoker		.057	1.559	.988	2.461
Moderate smoker		.556	1.138	.741	1.748
Heavy smoker		.000	4.450	2.610	7.587
Non-drinker (Ref group)	2	.185			
Moderate drinker		.868	1.035	.686	1.562
Harmful drinker		.129	1.370	.912	2.059
Stage 0 (Ref group)	4	.000			
Stage 1		.154	.450	.150	1.348
Stage 2		.857	.907	.312	2.633
Stage 3		.977	.984	.334	2.903
Stage 4		.278	1.779	.629	5.033
Lowest Income quintile (Ref group)	4	.883			
Quintile 2		.538	.826	.449	1.519
Quintile 3		.358	.709	.341	1.475
Quintile 4		.508	.772	.359	1.660
Highest Income quintile		.357	.676	.294	1.555
Most educated quintile (Ref group)	4	.358			
Quintile 2		.395	1.298	.712	2.365
Quintile 3		.531	1.243	.629	2.458
Quintile 4		.125	1.783	.851	3.737
Least educated quintile		.537	1.302	.564	3.008
CCI None (Ref group)	3	.298			
CCI Mild		.420	1.353	.649	2.822
CCI Moderate		.096	1.763	.904	3.439
CCI Severe		.245	1.544	.743	3.208
ECI None (Ref group)	3	.037			
ECI Mild comorbidity		.646	1.112	.708	1.747
ECI Moderate comorbidity		.006	1.886	1.205	2.952
ECI Severe comorbidity		.198	1.765	.743	4.192

Table 69 Final Cox Model of HNC type, age, stage, Income, Education, alcohol, smoking and ECI

Explanatory variables	df	Sig	HR	95% CI for HR	
				Lower	Upper
<40yrs (Ref group)	4	.204			
41-50yrs		.139	.148	.012	1.863
51-60yrs		.276	.282	.029	2.757
61-70yrs		.180	.205	.020	2.079
71 +yrs		.448	.409	.041	4.117
Non smoker (Ref group)	3	.003			
Ex smoker		.849	1.137	.305	4.231
Moderate smoker		.299	2.061	.527	8.060
Heavy smoker		.033	3.957	1.117	14.019
Non-drinker (Ref group)	2	.861			
Moderate drinker		.786	.873	.326	2.338
Harmful drinker		.935	1.044	.369	2.957
Stage 0 (Ref group)	4	.008			
Stage 1		.340	3.630	.256	51.368
Stage 2		.128	7.212	.567	91.697
Stage 3		.043	13.312	1.085	163.300
Stage 4		.032	16.217	1.263	208.237
Lowest Income quintile (Ref group)	4	.289			
Quintile 2		.394	.646	.236	1.767
Quintile 3		.227	.457	.128	1.629
Quintile 4		.101	.337	.092	1.235
Highest Income quintile		.030	.218	.055	.860
Most educated quintile (Ref group)	4	.014			
Quintile 2		.427	1.528	.537	4.343
Quintile 3		.009	6.304	1.583	25.105
Quintile 4		.001	10.163	2.443	42.271
Least educated quintile		.003	11.056	2.315	52.805
ECI None (Ref group)	3	.001			
ECI Mild comorbidity		.906	.937	.318	2.763
ECI Moderate comorbidity		.120	2.361	.799	6.975
ECI Severe comorbidity		.000	7.629	2.732	21.302

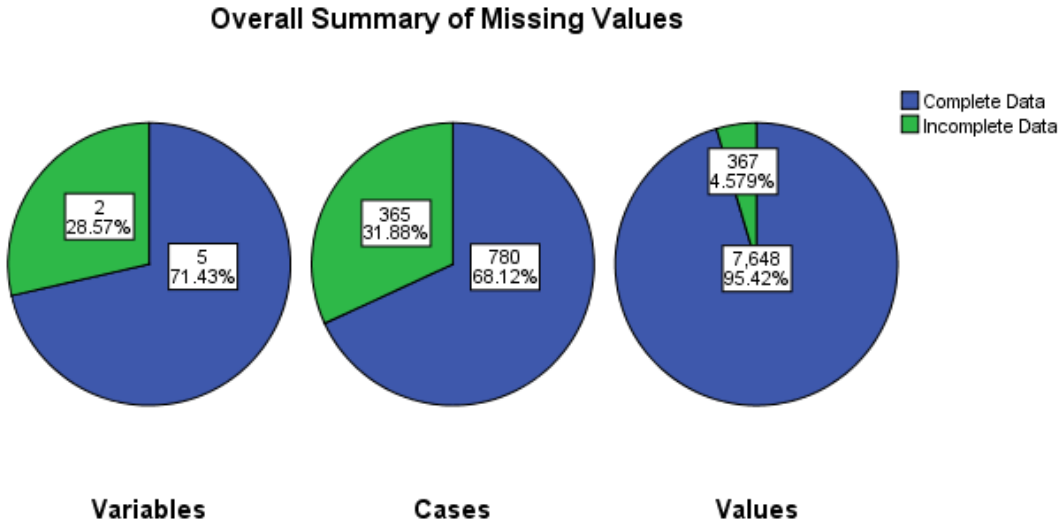
The model presented in Table 69 was able to clearly demonstrate the survival estimates as well as risk attenuation for the explanatory variables within the analysis. Heavy smokers had nearly 4 times an increased risk of death compared to non smokers (p=0.033). Patients with stage 3 disease were 13 times more likely to die (p=0.043) compared to those with stage 0 disease. Stage 4 patients were 16 times more likely (p=0.032) to experience reduced survival compared to stage 0 patients. Lower levels of educational attainment was also linked to poor survival, as Quintile 3

had a hazard of 6.304 (p-0.009), Quintile 4 had 10 times the risk (p=0.001), while the least deprived quintile had HR=11.056 (p=0.003). Only severe comorbidity demonstrated an association with poor survival with HR=7.629 which was highly significant with p<0.0001.

6.4.4. Multiple imputations of Full Cohort

As mentioned previously there were instances of missing data particularly for the Fife portion of the cohort. This data had been called prospectively as part of the patient records kept by the HNC Nurse Specialist. There were occurrences of missing data in important explanatory variables such as smoking and alcohol status, HNC type, SIMD income and education quintiles, TNM staging and sex. It was not clear exactly why there were missing data; however the missing values analysis shown below highlights the rationale for multiple imputations.

Figure 49 Missing values summary



The initial Cox proportional hazards regression model (Table 70) of the imputed data used Scottish SIMD and CCI. The risk prediction was unclear for all predictors except for moderate comorbidity which did demonstrate an elevation in risk of poor survival; however that result did reach statistical significance.

Table 70 Initial Cox Model of Scottish SIMD quintiles and CCI with MI data

Explanatory variables	SE	HR	95% CI for HR	
			Lower	Upper
Quintile 2	.257	.977	.590	1.618
Quintile 3	.284	.868	.495	1.521
Quintile 4	.236	.923	.580	1.467
Least deprived SIMD quintile	.285	.887	.507	1.551
CCI Mild	.436	1.293	.550	3.041
CCI Moderate	.425	2.702	1.174	6.219
CCI Severe	.535	.858	.301	2.447

Although there were some differences, the model (Table 71) including ECI and Scottish SIMD quintiles did show higher risk of death dependent on level of comorbidity or SES. In this model only moderate comorbidity was shown to have an effect on survival with HR=2.678 p=0.001.

Table 71 Cox Model of Scottish SIMD quintiles and ECI with MI data

Explanatory variables	SE	HR	95% CI for HR	
			Lower	Upper
Quintile 2	.264	.842	1.054	.628
Quintile 3	.272	.415	.801	.469
Quintile 4	.238	.815	.946	.593
Least deprived SIMD quintile	.293	.957	.984	.554
ECI Mild comorbidity	.245	.031	1.703	1.050
ECI Moderate comorbidity	.287	.001	2.678	1.505
ECI Severe comorbidity	.430	.685	1.192	.501

We then modified the analysis (Table 72) by adding all the other predictor variables to the analysis using Scottish SIMD quintiles and ECI comorbidity scores. This model showed an increase in risk of lower survival. Although there was no conclusive evidence for SES, we did nevertheless find that ECI moderate comorbidity was associated with poor survival with nearly with HR=2.298 (p=0.006).

Table 72 Cox Model of all variables + Scottish SIMD and ECI with MI data

Explanatory variables	SE	HR	95% CI for HR	
			Lower	Upper
Quintile 2	.292	.662	1.137	.636
Quintile 3	.284	.700	.896	.513
Quintile 4	.244	.903	1.030	.638
Least deprived SIMD quintile	.314	.717	.892	.481
Sex	.184	.652	1.087	.757
ECI Mild comorbidity	.258	.295	1.311	.787
ECI Moderate comorbidity	.296	.006	2.298	1.280
ECI Severe comorbidity	.430	.685	1.192	.501

The earlier systematic review conducted as part of the thesis had found that income and education had a significant impact on survival. This finding was tested in the combined cohort using SIMD income and education quintiles with ECI as well as the other predictors (Table 73). We could not find an association with poor survival in this iteration.

Table 73 Cox Model of all variables + Income, education quintiles and ECI with MI data

Explanatory variables	SE	Sig	HR	95% CI for HR	
				Lower	Upper
Income Quintiles	.128	.768	.963	.743	1.247
Education Quintiles	.146	.251	1.187	.879	1.603
Sex	.183	.718	1.068	.746	1.529
ECI Mild comorbidity	.267	.302	1.320	.775	2.248
ECI Moderate comorbidity	.282	.002	2.397	1.376	4.173
ECI Severe comorbidity	.435	.979	1.012	.421	2.432

In the next step we conducted the same analyses as before but this time we replaced ECI with CCI in order to see if this would provide a better model of predicting premature mortality. The outputs are depicted in the following 4 tables, (Table 74-77).

Table 74 Cox Model of income, education and CCI with MI data

Explanatory variables		SE	Sig	HR	95% CI for HR	
					Lower	Upper
Original data	Income Quintiles	.108	.841	.841	.978	.791
	Education Quintile	.114	.266	.266	1.134	.908
	CCI None/Mild (Ref)		.000	.000		
	CCI Moderate	.433	.549	.549	1.296	.555
	CCI Severe	.422	.018	.018	2.714	1.187
Pooled data	Income Quintiles	.112	.980	.980	1.003	.805
	Education Quintiles	.120	.411	.411	1.104	.871
	CCI Mild	.433	.556	.556	1.290	.552
	CCI Moderate	.422	.018	.018	2.705	1.774
	CCI Severe	.531	.794	.794	.871	.308

b. Constant or Linearly Dependent Covariates CCI (3) =0

The analysis illustrated in Table 74 did not demonstrate a modification of the approximation of survival once the data imputations had been conducted. The original data showed a HR of 2.714 (p=0.018) in the severe comorbidity group but this was no longer evident after the multiple imputations.

Using SIMD income and education domains showed improved prediction of survival with higher hazard ratios noted within the model (Table 75). The CCI moderate comorbidity group showed an elevation in risk of death with HR=2.418 (p=0.043).

Table 75 Cox Model of all variables, Income, education and CCI with MI data

Explanatory variables	SE	Sig	HR	95% CI for HR	
				Lower	Upper
Income Quintiles	.114	.878	.983	.784	1.232
Education Quintiles	.126	.440	1.103	.858	1.417
CCI Mild	.445	.814	1.110	.464	2.655
CCI Moderate	.436	.043	2.418	1.029	5.683
CCI Severe	.540	.419	.647	.225	1.862

b. Constant or Linearly Dependent Covariates Charlson(3) = 0 ;

However in comparison, when assessing the prognostic impact of the predictor variables, ECI status and SES measured using the Scottish SIMD quintiles, there was evidence that both comorbidity and SES affected survival (Table 76). This model could not demonstrate the influence of either SES or comorbidity in determining survival within the cohort.

Table 76 Cox Model of all variables, Scottish SIMD and CCI with MI data

Explanatory variables	SE	Sig	HR	95% CI for HR	
				Lower	Upper
Quintile 2	.273	.436	1.237	.724	2.114
Quintile 3	.313	.979	.992	.533	1.847
Quintile 4	.252	.867	1.043	.636	1.712
Least deprived SIMD quintile	.309	.626	.860	.469	1.576
CCI Mild	1.613	.249	.151	.006	3.968
CCI Moderate	1.609	.325	.201	.008	5.214
CCI Severe	1.586	.114	.078	.003	1.883

6.5. Key findings

There were initial methodological challenges in conducting the survival analysis of the Fife and Tayside data due to missing data particularly in the Fife cohort. These data did not appear to follow any patterns of missingness i.e. the data were missing at random, therefore multiple imputations were used to fill in the missing values were conducted. The two regions showed an approximately 2:1 ratio of HNC occurrence in males compared to females. Most of the HNC cases occurred in patients aged 60 years and above with the majority of HNCs being laryngeal cancers. Cross tabulations of disease stage and SES showed that more advanced cancers were diagnosed in the lower SES (deprived groups).

In the evaluation of cumulative survival distributions, there were contrasting findings by region particularly for age, HNC Type, smoking status, CCI, ECI, SIMD quintiles, as well as the income and education quintiles (Table 77).

Table 77 Comparison of survival between Fife and Tayside

Explanatory variable	Highest survival group (Fife)	Mean survival time (Fife)	Highest survival group (Tayside)	Mean survival time (Tayside)	Lowest mean survival group (Fife)	Mean survival time (Fife)	Lowest mean survival group (Tayside)	Mean survival time (Tayside)
Age	71+years	3611.622	41-50years	2248.349	41-50years	3118.196	71+years	1339.626
Gender	Males	3560.259	Males	1761.854	Females	3519.176	Females	1744.859
HNC Type	Laryngeal cancer	4165.917	Nasopharyngeal cancer	2020.625	Nasopharyngeal cancer	2346.202	Hypopharyngeal cancer	985.673
Stage	Stage I	3779.726	Stage I	2195.024	Stage IV	2835.671	Stage IV	1429.393
Alcohol status	Moderate drinker	3266.742	Moderate drinker	2014.195	Hazardous drinker	2842.768	Hazardous drinker	1735.148
Smoking status	Never smoked	3643.577	Never smoked	2183.709	Moderate smoker	2915.017	Heavy smoker	1631.218
CCI	No comorbidity	4077.387	Moderate comorbidity	1932.934	Severe comorbidity	3132.877	Severe comorbidity	1448.493
ECI	Moderate comorbidity	3719.195	No comorbidity	1842.576	Severe comorbidity	2292.500	Severe comorbidity	530
SIMD quintiles	Least deprived	3573.006	Least deprived	1717.805	Quintile 4	2994.637	Most deprived	1590.289
SIMD education quintiles	Quintile 2	3797.331	Most educated	1833.497	Least educated	3190.224	Quintile 4	1491
SIMD Income quintiles	Highest income	3903.894	Quintile 3	1965.660	Lowest income	3164.602	Lowest income	1567.818

We found that survival distributions for age contrasted between the two regions as in Fife patients aged 71 years and older had better survival than their younger counterparts, and this same age group had the worst mean survival times in the Tayside cohort. Those age 41-50 years appeared to fare better in Tayside with the highest mean survival time, however this group had the worst survival amongst the Fife patients. These results were unexpected as the risk of death did not follow the expected age gradient in Fife although the reason for this difference was not immediately clear.

There were regional variations for HNC Type as laryngeal cancer patients fared better than those diagnosed with nasopharyngeal cancer in Fife. In contrast, the Tayside patients diagnosed with nasopharyngeal cancer had best mean survival figures in comparison to other forms of HNC while those with cancer of the hypopharynx appeared to have the worst survival outcomes.

For smoking status, we found the disparity in that moderate smokers from Fife experienced the lowest survival as did heavy smokers in the Tayside group. There were differences in outcomes based on CCI, with patients without comorbid disease having the best outcomes. This result was not similar to the outcome in Tayside where patients with moderate comorbidity had the better prognosis. In contrast for ECI measured comorbidity, it was the moderate comorbidity group that had better survival figures in the Fife cohort and in Tayside patients classified as having no comorbidity fared better than all other comorbidity categories.

In terms of SES, we noted that differences between groups were also evident. For the SIMD quintiles we found that Fife patients from Quintile 4 had the worst outcomes as did the most deprived patients within the Tayside cohort. In Fife patients from Quintile 2 had the best mean survival time as did the Tayside patients from the most educated quintile. For the worst survival outcomes, in Fife patients from Quintile in Fife and the most educated Tayside had the best prognosis. For those with the worst mean survival, the least educated and those from Quintile 4 from Fife and Tayside respectively were noted to have the lowest mean survival times. Prognosis

was favourable for Fife patients classified as highest income quintile while the Tayside patients from Quintile 3 had the best survival outcomes.

The cumulative survival distributions were able to present evidence of factors such as the type of HNC, disease stage; alcohol intake and smoking are linked to survival in HNC. Empirical evidence has shown that laryngeal cancers have the best prognosis in HNC as they have high cure rates. (464, 465) However despite this Tayside appeared to buck this trend. The results for disease stage and alcohol status were unremarkable and similar to those confirmed elsewhere, i.e. patients with stage I disease have the better prognosis and those with stage IV have the highest risk of death. (267) (466) Moderate alcohol intake has long been linked with more favourable outcomes in cancer patients and this appeared to be the case for patients classified as moderate drinkers in both Fife and Tayside. (467-471)

Smoking has been noted as a significant aetiological factor in HNC and the heavier the smoking, the higher the risk of poor HNC outcomes. In the Fife cohort the survival distributions showed that moderate smokers had the worst survival. This finding is contrary to the research findings that noted a dose-response relationship for smoking in HNC. (33, 77, 472-482) The SIMD income and education had a less clear pattern of survival distribution particularly for the education domain which showed that the Quintile 4 patients had the worst survival, meaning that the least educated had better mean survival times. It is not apparent why this particular group did not have the expected survival distribution of those with the lowest educational attainment having the worst prognosis, (126, 483-485) A finding that has been confirmed in oesophageal cancer. (486)

The table (Table 78) depicts the variation in Cox proportional hazard regression analyses conducted on the two regions. These results show that the Tayside data was able to provide more reliable estimates of risk when compared to the Fife dataset. These effects were clearly demonstrated for smoking status which showed a clear statistically significant elevation in risk

for a corresponding increase in smoking levels; moderate smokers HR= 2.825 (p=0.051), heavy smokers HR= 3.885 (p=0.005).Only stage 4 disease showed a high risk of death, HR=2.659 (p=0.049), as did severe comorbidity measured using the ECI with HR=3.052 (p=0.030).

It would appear that multiple imputations in the Fife data did not enhance the predictive potential as the results were unable to show whether comorbidity or SES were linked to survival. This was unexpected as the initial analysis had shown that both prognostic factors affected survival. It is not clear why the imputed Fife data could not provide meaningful conclusions. Another issue worth pointing out is that the CCI was shown to have limited capacity for predicting survival as the hazard ratio did not achieve statistical significance. Initially there was evidence of confounding from age which makes sense as the CCI score incorporated age. In subsequent analyses age was dropped from the analysis; however this did not improve matters. On its own CCI measured comorbidity could not provide meaningful results but when combined with the ECI, an increase in the hazard was noted for ECI; therefore CCI appeared to amplify the effect of ECI. This may be due to the fact that ECI incorporates other conditions which are not included in the CCI.

Table 78 Risk of death comparison between Fife and Tayside

Explanatory variables	Sig (Tayside)	HR (Tayside)	95% CI for HR	
			Lower (Tayside)	Upper (Tayside)
Non-smoker (Ref)	.774 (.021)			
Ex-smoker	.605 (.120)	.839 (2.172)	.430 (.817)	1.635 (5.776)
Moderate smoker	.751 (.051)	1.119 (2.825)	.560 (.993)	2.234 (8.033)
Heavy smoker	.807 (.005)	.923 (3.885)	.483 (1.502)	1.763 (10.045)
Non-drinker (Ref)	.292 (.387)			
Moderate drinker	.463 (.109)	.785 (.565)	.411 (.281)	1.499 (1.135)
Harmful drinker	.731 (.650)	1.114 (.811)	.602 (.328)	2.061 (2.004)
Hazardous drinker	.304 (.436)	1.340 (.741)	.767 (.349)	2.340 (1.574)
Stage 0 (Ref)	.001 (.000)			
Stage 1	.320 (.411)	.347 (.621)	.043 (.200)	2.801 (1.932)
Stage 2	.673 (.845)	.640 (1.113)	.080 (.381)	5.093 (3.256)
Stage 3	.858 (.492)	.827 (1.479)	.104 (.484)	6.606 (4.522)
Stage 4	.802 (.049)	1.298 (2.659)	.170 (1.006)	9.935 (7.031)
Lowest Income quintile (Ref)	.763 (.831)			
Quintile 2	.556 (.949)	1.400 (.973)	.456 (.421)	4.293 (2.248)
Quintile 3	.995 (.377)	1.003 (.626)	.397 (.221)	2.535 (1.772)
Quintile 4	.422 (.576)	.757 (.733)	.383 (.246)	1.495 (2.180)
Highest Income quintile	.831 (.364)	.943 (.571)	.552 (.170)	1.611 (1.917)
Most Educated quintile (Ref)	.354 (.477)			
Quintile 2	.886 (.949)	1.079 (.972)	.382 (.399)	3.050 (2.364)
Quintile 3	.656 (.368)	1.232 (1.600)	.493 (.575)	3.078 (4.448)
Quintile 4	.642 (.139)	.825 (2.359)	.367 (.758)	1.855 (7.346)
Least Educated quintile	.133 (.336)	1.505 (1.857)	.883 (.527)	2.567 (6.540)
ECI No comorbidity (Ref)	.033 (.114)			
ECI Mild comorbidity	.045 (.365)	.532 (1.378)	.288 (.689)	.986 (2.758)
ECI Moderate comorbidity	.440 (.125)	1.235 (2.013)	.723 (.823)	2.111 (4.923)
ECI Severe comorbidity	.052 (.030)	.226 (3.052)	.050 (1.112)	1.012 (8.376)
CCI No comorbidity (Ref)	.002 (.122)			
CCI Mild comorbidity	.896 (.563)	.939 (.747)	.368 (.278)	2.401 (2.008)
CCI Moderate comorbidity	.551 (.630)	1.238 (1.284)	.613 (.464)	2.500 (3.552)
CCI Severe comorbidity	.008 (.831)	.943 (.571)	.552 (.170)	1.611 (1.917)

We found that comorbidity measures identified both alcohol and smoking related comorbidities namely, ECI found rates of 5.6% for alcohol abuse, 4.3% for liver disease, while CCI had 3.8% for mild liver disease, 10.5% for myocardial infarction and 6.4% for peripheral vascular disease. The presence of comorbidities may also be due to the relationship there a large proportion of the

cohort were as older patients, who tend to develop more chronic age related conditions. This assumption was substantiated through cross tabulations.

In the combined model of the Fife and Tayside patients using all the explanatory variables, there was significant synergistic effect of both Elixhauser measured comorbidity and SIMD income and education measured SES in overall survival for HNC. Table 79 shows the multivariate model of the Full cohort and how smoking, alcohol and stage contributed to the analysis of survival. This model showed that both education and ECI measured comorbidity were associated with survival in the Full cohort. Smoking and alcohol consumption are important aetiological factors for HNC which have also been found to affect survival after diagnosis. (270, 310, 361, 392, 481, 487-492)

Table 79 Cox model of Full cohort

Explanatory variable	df	Sig	HR	Lower 95%CI	Upper 95% CI
Ex smoker		.849	1.137	.305	4.231
Moderate smoker		.299	2.061	.527	8.060
Heavy smoker		.033	3.957	1.117	14.019
Non-drinker (Ref group)	2	.861			
Moderate drinker		.786	.873	.326	2.338
Harmful drinker		.935	1.044	.369	2.957
Stage 0 (Ref group)	4	.008			
Stage 1		.340	3.630	.256	51.368
Stage 2		.128	7.212	.567	91.697
Stage 3		.043	13.312	1.085	163.300
Stage 4		.032	16.217	1.263	208.237
Most educated quintile (Ref group)	4	.014			
Quintile 2		.427	1.528	.537	4.343
Quintile 3		.009	6.304	1.583	25.105
Quintile 4		.001	10.163	2.443	42.271
Least educated quintile		.003	11.056	2.315	52.805
ECI None (Ref group)	3	.001			
ECI Mild comorbidity		.906	.937	.318	2.763
ECI Moderate comorbidity		.120	2.361	.799	6.975
ECI Severe comorbidity		.000	7.629	2.732	21.302

In the full cohort and in the individual predictor models, the effect of both comorbidity and SES did have an effect but this was amplified when all the other predictors (HNC type, smoking, alcohol, gender, stage and age) were added to the model.

In terms of smoking status and comorbidities, the survival analysis results presented in this chapter did show that patients classified as heavy smokers had more severe comorbidities. The Tayside data was able to give more clarity to the disproportionate risk of premature death posed by increasing severity levels of comorbidity. This was more apparent for comorbidity that was measured using the ECI in combination with Scottish SIMD income and education quintiles, as this more apparent for mild and severe comorbidity in proportional hazards modelling that adjusted for all the important explanatory variables i.e. HNC type, age, stage, smoking and alcohol status. Laryngeal and oropharyngeal cancers were shown to have the most favourable outcomes, while hypopharyngeal cancers were associated with higher likelihood of premature mortality. Heavy smoking was also linked to excess mortality while no relationship could be elicited for alcohol status.

In this study, there were a higher number of men who were diagnosed with HNC, which represented an approximate 2:1 ratio of incidence in males compared to females. Evidence of a higher incidence of HNC from the 6th decade of life onwards for most of the patients was observed in this study. More HNC patients had advanced disease with a greater number coming from deprived backgrounds which would appear to be a substantiation of the theory of lower SES (deprivation) being associated with patients presenting with more advanced disease.

HNC type was found to have a significant influence on survival. Nasopharyngeal cancers were noted to have a high risk of mortality compared to the other forms of HNC within the cohort. The increased hazard of death was particularly apparent for patients with severe comorbidity and from deprived backgrounds who were shown to have an elevated risk of death compared to patients who had no comorbidity and came from less deprived backgrounds. These findings are consistent with the initial hypothesis and a prior systematic review we found that the association between comorbidity, SES and overall survival was stronger for patients with severe comorbidity and from the most deprived quintiles. The simultaneous occurrence of comorbidity and HNC is

known to increase with age and with the typical HNC patient also coming from a deprived background, this clustering of disadvantage poses significant challenges to the clinical course of the disease and patient outcomes. Interestingly the systematic review reported in an earlier chapter of this thesis had noted that age and SES had an interaction but when this was tested using proportional hazards methods an increased risk was noted for younger patients although the relationship was less clear for SES.

The influence of comorbidity was assessed using the ECI and this was found to be a better predictor of mortality compared to the CCI with AIC statistics of 6089.35 for ECI and 6089.769 for CCI. The rationale for selecting the ECI is had the smaller AIC which meant that ECI fit the cohort data better. The AIC score focuses on the strength of evidence, and gives a measure of uncertainty for each model. In contrast, conventional model selection approaches such as backward, forward, or stepwise selection procedures are generally based on hypothesis tests, where at a certain P -value, a variable is included or excluded. These techniques often yield different conclusions depending on the order in which the models are computed, whereas the AIC approach yields consistent results and is independent of the order in which the models are computed. ECI was chosen before CCI as it had more reliable estimates of survival based on the AIC which was greater for the former compared to the latter. The findings of this analysis are useful to frontline clinicians as they can use them to match patient characteristics within the context of HNC as closely as possible in order to ascertain the risk profile for each patient. This means that the clinical team have to collect comorbidity and SES data alongside other demographic variables upon the patient's first presentation in order for the methods reported here to be useful in allowing them to conduct a more accurate prediction of survival.
In addition to the statistical evidence advocating the use of the ECI to measure comorbidity within a cohort; a systematic review and comparative analysis (493) was able to demonstrate that among various comorbidity indices, ECI is a better predictor of survival when compared to the CCI.

6.6. Chapter summary

In this chapter the results of the survival analysis of the original data and the imputed data were presented. There were 1344 patients in a cohort that was derived from HNC patients residing in Fife and Tayside. 533 deaths were recorded and HNC accounted for 42% of these deaths. Methods to account for missing data were used in order to allow for more robust survival analysis. The key predictors were ECI measured comorbidity, stage, smoking status, SIMD income and education quintiles. We were able to demonstrate the importance and impact of both comorbidity and SES in survival and this was particularly the case in the Tayside cohort. Although the Fife data had more patient numbers, the datasets validity was reduced by missing data. Chapter 7 will discuss the key findings of this thesis. It will compare the results of Chapter 6 with other empirical findings. This chapter will analyse the methods used to answer the research questions and analyse the data in order to identify any strengths and weaknesses.

Chapter 7

7.1. Discussion

7.1.1. Chapter Outline

This chapter will bring together all the information presented in this thesis and by evaluating the results presented in Chapter 6, discuss these within the context of their association with findings from the systematic review (Chapter 2). The contribution of the development of a QA tool (Chapter 3) will be examined alongside a discussion of whether the information presented in the thesis supported the hypothesis. The soundness of methods employed to conduct data linkage will also be under consideration. A debate on how the results were presented as well as how the results relate to the research questions will also be conducted. The strengths and weaknesses will be debated alongside the consideration of whether any inferences of the findings could be made in order to modify clinical practice.

7.2. Discussion

In order to answer the research questions, the principal investigator began by seeking empirical evidence of how both deprivation and comorbidity act or interact to affect HNC survival. This began with a systematic review which found that both these two factors appeared to affect survival. Increasing comorbidity and deprivation were associated with a greater risk of mortality for HNC patients. However almost all studies reported on one factor only, so there was limited evidence of the interplay between them. A key issue was how to critically appraise and assess the quality of the primary research studies reported in the systematic review of the literature. Due to the lack of a suitable existing tool, a methodological quality assessment tool was developed to appraise the studies included in the systematic review. In order to test whether the results from the review could be validated using a sample of patients from Scotland, a retrospective data

analysis of patients from Fife and Tayside was carried out. The analysis found a linear association between deprivation and comorbidity illustrating that patients from deprived backgrounds measured using SIMD and with severe comorbidity measured using the ECI rather than CCI had lower survival compared to their counterparts. The results for the Tayside cohort were largely similar results to those of the systematic review as the data was more complete. When the analysis used the combined data, surprisingly the findings were less clear for the SIMD domains of income, although education did appear to be linked to survival.

The results of the survival analysis pointed to the key prognostic importance of both comorbidity and SES in determining the survival of patients diagnosed with HNC. It was clear that the ECI performed better than the CCI as the parameter estimates demonstrated a marked change when the ECI was introduced into the survival analysis. The Fife data had limited validity due to issues of missing data for the key predictors however this shortcoming was addressed through multiple imputation methods. The full cohort analysis was able to demonstrate the dose-response relationship of important predictors such as stage, smoking and alcohol in estimating survival as comorbidity and educational attainment were shown to have a significant impact on HNC survival.

In terms of SES (using income and education domains), the survival analysis showed that patients from deprived backgrounds had lower survival. We were also able to demonstrate that deprived patients from both regions presented with more advanced tumours, while the type of cancer was also shown to have an important role in predicting survival with laryngeal cancers having better outcomes when compared to mouth cancers. These findings gave similar results to the systematic review with evidence of a declining survival gradient dependent on comorbidity severity and the SIMD also income and education particularly; having a detrimental effect on survival for those patients from low SES backgrounds.

Both the systematic review conducted at the beginning of this thesis and the analysis of a homogenous cohort of patients from Fife and Tayside assessed the prognostic capacity of two factors; comorbidity and SES. We were able to ascertain that comorbidity and SES are important prognostic factors in HNC. The Tayside data was more complete and therefore was able to demonstrate a strong dose response relationship for this association showing that both factors contribute a multiplicative risk of reduced survival prospects. The systematic review was able to confirm that increasing comorbidity was associated with worse survival and that low income and low educational attainment were also linked to poor survival outcomes. The retrospective cohort analysis found that only moderate and severe ECI measured comorbidity were independent risk factors for overall survival in multivariate analysis. The reduction in survival probability became more pronounced when CCI scores were used in the analysis in addition to ECI. Despite there being limited prognostic capacity of the CCI, the results obtained from both the systematic review and the cohort study point to the importance of these findings as well as their clinical implications.

In terms of the measurement of SES, the initial approach of using Scottish SIMD deciles was found to be cumbersome. The Scottish SIMD quintiles were also considered, however as the systematic review had noted how both income and education were appropriate measures to approximate SES this was considered a superior method of classifying SES. In the retrospective cohort analysis, the SIMD findings were not as pronounced as those for the income and education domains therefore we have reported on these because they were found to be the best method of SES measurement.

7.3. Comparison with the literature

There is a plethora of evidence confirming a link between poor HNC survival, based on prognostic factors such as comorbidity and SES. The results presented in this thesis showed that severe

comorbidity had a significant impact on survival. The survival estimates based on comorbidity level and SES found in this study are broadly similar to findings from other studies. These studies showed a significant relationship between comorbidity severity and survival. (10, 139, 150, 156, 160, 294, 494, 495) Datema *et al* (330) confirmed this by creating a risk model to predict survival for newly diagnosed HNCs. After adding comorbidity, a substantial comorbidity impact on overall survival was observed with the worst outcomes predicted for severe comorbidity. (496) Better survival was noted for mild or no comorbidity groups, (333, 497). Table 80 presents the Tayside cohort analysis results from this thesis in comparison to those of four studies that were included in the systematic review presented in Chapter 2.

Table 80 Comparison between this study & systematic review studies

Study author & country	Type of HNC	Measurement method	Magnitude of effect (HR)
This study Scotland	All HNCs except thyroid	Comorbidity: ECI & CCI	ECI None HR=1.0 Mild HR=1.676 (CI 1.059;2.632) Moderate 2.941 (CI 1.801;4.802) Severe HR=4.134 (CI 1.712;9.644) CCI None/Mild HR=1.0 Moderate HR=1.341 (CI 0.571;3.149) Severe HR=2.821 (CI 1.226;6.486)
Teppo Finland	Larynx, tongue and pharynx	Comorbidity: CCI	Low comorbidity HR=1.0 Modest HR=0.9 (CI 0.4,2.2) High HR=5.6 (CI 2.3,13.5) p<.001
Piccirillo USA	Head and neck	Comorbidity: ACE-27 Index	No comorbidity HR=1.00 Mild HR=1.03 (CI 0.80,1.32) Moderate HR=1.92 (CI 1.50,2.47) Severe HR=2.48 (CI 1.77,3.47) p<.001
Yung USA 2008	Oral cavity, oropharynx and larynx	Comorbidity: ACE-27 Index	None to mild 1.4 (CI 0.4-5.3) None to moderate 1.7 (CI 0.4-6.7) None to severe 3.4 (CI 1.1-10.1)
Homma Japan 2009	Hypopharynx	Comorbidity	None-Mild 1.80 (CI 1.21, 2.68) p=.0036 Moderate-Severe 1

We could not find any previous empirical investigating the same prognostic effect of comorbidity and SES in HNC. The only reviews we found were on comorbidity only (304) (11) and SES, (194) however the latter review had methodological flaws. (195-197) There was no evidence of similar research being previously conducted within the HNC field, however a similar study reviewing the survival of patients from deprived backgrounds with comorbid disease had been carried out in

colorectal cancer. (145) Therefore due to the paucity of research in this field of oncology, we embarked upon the SR and subsequent retrospective cohort analysis.

Interestingly a recent systematic review by Boeje *et al* (11)showed that comorbidity is a strong predictor of survival confirming findings from Habbous *et al* (392)and Peters *et al* (10). These previous research studies point to the validity and applicability of our findings in the prognostication of HNC. Comorbidity is a common occurrence in HNC (258, 498) and severe comorbidities increase the risk of death as treatments have to be adapted meaning patients are at higher risk of death as confirmed elsewhere. (16, 499) This relationship between severity of comorbidities and outcome has been found in different cancer sites, including head and neck cancer, (138, 500) breast, (501, 502) ,prostate, (503, 504) and colon cancer,(100, 505) among others.

The CCI has been validated to be applicable in the evaluation of head and neck cancer (163), however there has been one previous attempt to validate the ECI within HNC (506) although this has been conducted in other diseases. (441, 443, 446, 493, 507, 508) Our results revealed that CCI and ECI were useful prognostic indicators for comorbidity and should be widely applied in the evaluation of comorbidities. Previous researchers had shown that the ECI is a superior method of comorbidity measurement compared to the CCI. (441, 443, 444, 493, 507-511)This study was able to establish that the ECI was the best possible method for comorbidity measurement (Tables 39, 43-46, 50-52, 54, 65-71, 73-75) after comparison of survival estimates between ECI and CCI, it was noted that the ECI used more conditions that impact HNC survival such as weight loss and therefore it was deemed that this index was able to provide more reliable estimates of risk.

When considering the prognostic contribution of comorbidity using the ECI in the cohort analysis, there was evidence of an association between severe levels of comorbidity and an increase in risk of death from all causes. The ECI appeared to be superior in predicting mortality when compared against the CCI. In most of the models, the findings of the ECI achieved better statistical

significance while CCI did not. This supports research studies that have shown that the ECI performed better than CCI in other conditions such as colorectal cancer (443), orthopaedics (508), coronary artery bypass graft surgery (493), myocardial infarction (493, 507), and stroke(493) among others in calculating risk of death. In terms of the impact of SES on survival, there was evidence showing that HNC survival was strongly correlated with SES as lower SES groups had higher incidence of mortality compared to higher SES groups. (108, 212, 360, 362, 363, 372, 426, 512-514)

According to our findings, smoking and alcohol status played an important role in the survival of HNC patients. It has been hypothesised that low SES (deprived) backgrounds may mediate poor lifestyle behaviours such as smoking and drinking. The lifestyle factors of smoking and alcohol status were both shown to be linked to increased mortality; and smoking especially had a statistically significant effect on survival and in this cohort there was a strong association between smoking status and SES with the low SES patients predominantly found in the heavy smoker group. It would appear from this data that both smoking and alcohol did not have an independent effect on survival as they are both closely linked to SES. There is evidence to show that smoking and alcohol may have amplified the effect of both prognostic factors as excessive smoking and high alcohol consumption have previously been identified as the main risk factors of HNC.(123, 179, 194, 306, 473, 491, 515, 516) (34, 477, 481, 489, 517-519)

There is empirical evidence pointing to low SES being linked to a lack awareness of the symptoms of HNC (112, 520, 521) and that patients from deprived backgrounds tend to present with more advanced disease. (522-525) Conversely there is an emerging trend in HNC that has pointed to better overall survival for younger HNC patients due to their HNC being caused by HPV. (27, 31, 32, 60, 526-528) Additionally age related complications that tend to occur at higher rates in older age groups have also been shown to contribute to these survival disparities. (495) (79, 256, 272, 529) Our systematic review (Chapter 2) found that younger patients with severe comorbidity had

worse outcomes, but this finding was not evident in the analysis of the retrospective cohort. We did however find that death from all causes was higher due to comorbidities, a finding echoed in previous HNC studies, (17, 530, 531) and also in cancer of the prostate, (206, 446, 506, 532) lung cancer (533), colorectal cancer (534) (145), renal disease, (535) breast cancer, (536, 537) and non-Hodgkin lymphoma. (538)

This thesis has been able to investigate the prognostic influence of SES and has found survival disadvantage for patients from deprived backgrounds. Specifically, the individual SIMD domain scores for income and education which had been identified in the earlier systematic review as good predictors of mortality were also found to have clinical importance within the cohort under study. This supports existing empirical evidence that identified reduced survival probabilities for patients with severe comorbidity and low SES. In terms of SES, it's influence has been confirmed in other cancer sites namely, oesophageal cancer (486, 539), prostate cancer (540), gastric cancer (541, 542), lung cancer and cancers of the upper aero-digestive tract (543), colorectal cancer (144) and breast cancer.(544) In spite of a disproportionate burden of disease being noted for males compared to females, (543), there was little evidence of a socioeconomic gradient to this.

There is a strong gradient of increasing incidence with deprivation in tumours of the head and neck. (545) (110, 123, 183) This is particularly the case for cancers of the oral cavity (183, 545), oropharynx and larynx. (545) Cancer survival as determined by SES has received attention from researchers previously with SES defined using income level data or level of education while others have employed proxy measures such as occupation and particularly in America, health insurance status. (309, 540, 546) Patients of low SES and of more advanced age have a higher likelihood of having comorbidity. This may be due to risky lifestyle behaviours such as smoking and drinking. Brusselaers *et al* (486) found that higher education levels had improved survival compared to the less well educated in oesophageal cancer.

Although the individual SIMD domains did not consistently show evidence of statistical significance, the difference in survival probabilities between the groups show that income and education have prognostic importance and clinical relevance. This finding had been confirmed in the systematic review conducted prior to the retrospective data analysis. Patients from least deprived quintiles were noted to have better survival compared to their most deprived counterparts in the median survival distribution in Kaplan-Meier, univariate and multivariate analysis. In the Cox proportional hazards regression model, both comorbidity and low SES measured by SIMD income and education quintiles demonstrated increase in the risk of mortality.

In terms of the influence of type of HNC on outcomes, this study had found that cancers of the nasopharynx had poor survival compared to cancers from other sites within the head and region. These study findings agree with empirical evidence that cancers of the oral cavity (mouth cancer), oropharynx and larynx have better outcomes. (149, 164, 262, 547) SES has previously been confirmed as a predictor of survival, something which this thesis has been able to corroborate.

7.4. Strengths of the study

This is the first attempt to systematically review and seek confirmation of systematic review findings by conducting a retrospective cohort evaluation of how both comorbidity and SES can affect survival. These findings suggest that people with severe comorbidity from low SES backgrounds have an excess risk of mortality and a significant attenuation in risk is apparent following adjustment for covariate variables. The systematic review provided a summary of the empirical evidence on this subject, while the cohort analysis was used to confirm whether the systematic review findings could occur in a cohort from two distinct geographic regions of Scotland.

The methodological QA tool was a key strength of this thesis as it is an excellent instrument which was validated as suitable for use with the cohort in the latter part of this thesis. The tool was developed to quality appraise survival studies which is very different from reporting checklists such as MOOSE. The tool helped to assess the adequacy of the methods used to conduct the primary study. This appraisal of study quality was then used to construct a quality score or rating of the methodological quality of each study. In contrast MOOSE is an example of study reporting guidelines which allow researchers to give clear and accurate accounts (full information) of the study methods and findings. It allows peer reviewers to assess the adequacy of reporting, allow assessment of risk of bias and is now considered as a key to the value of a research publication which further enhances the project as the systematic review used these guidelines to report the review results. This demonstrates a link between study reporting guidelines and their link to critical appraisal. Additionally, inclusion of studies into meta-analysis hinged on the quality of reporting and homogeneous measurement methods and by using the MOOSE guidelines to support the QA of included studies, this thesis was able to ensure that study methods showed relevance, reliability, validity and are reproducible where applicable i.e. in the retrospective cohort analysis.

The methods used to create the patient cohort were ideal at selecting eligible HNC cases from the two geographic regions of interest. The sources of the linked health datasets were derived from sources within the NHS which provided a robust and valid patient pool. It is therefore likely that deaths of those patients who had migrated out of Fife or Tayside could be identified easily. These data corroborate earlier studies and clearly demonstrate the effect on survival of comorbidity and SES in HNC patients. The major strengths are that this is a much larger cohort than most previous studies with 1145 patients from two distinct geographic regions of Scotland. In addition, this thesis has been able to identify robust SES and comorbidity measures, which were tested during the data analysis and held up well as sound predictors of mortality risk.

A key strength from this study is that we used linked administrative health data in order to create the dataset we analysed. This method is a more robust technique of assessing comorbidity status in a cohort as compared to chart review. (438, 444, 548-550) This study had several strengths as we used two centres to assess the prognostic impact of comorbidity and SES. We had a diverse group of HNC patients of various ages, HNC subtypes and disease stage and were able to assess the prognostic influence of both factors. The findings presented here advocate the assessment of comorbidity and SES in planning treatments and management of HNC with the ultimate goal of improving survival outcomes.

A key point to note is the differences in the cohort sizes which is unexpected as Tayside is a much bigger geographical area than Fife and has a larger population, so one would expect a much larger cohort. The Tayside cohort is much smaller than that from Fife because it was made up the data collected between the Oral/Maxillofacial, ENT and oncology teams at Ninewells Hospital. ISD Cancer Registry statistics show a higher incidence of HNC in Tayside, however as there had not been a formal process for prospective data collection between the teams mentioned peviously, the records are fewer. However despite this appearing to be a shortcoming the inclusion of the Fife data which the Head and Neck Cancer Nurse Specialist began collecting prospectively upon commencement of her post in the late 90s made the data reported here the largest retrospective cohort analysis of this kind in Scotland. The results from survival analysis largely correspond with data from the Cancer Registry, with factors such as SES, type of HNC, stage, TNM classification having an impact on survival. The data reported in this thesis are more robust than the cancer registry data as the data linkage with SMR01 made it possible to use more in depth data on HNC subsite, comorbidity and SES measured using the Scottish SIMD quintiles in addition to SIMD income and education domain scores. The analysis data unravelled the complex interplay between tumour and patient factors in determining survival in HNC.

We used composite scores for both Charlson and Elixhauser, a composite score is the summary score after adding the relevant weights for each comorbidity to get a final score that helps with predicting survival of patients. The rationale is that a composite score or summary score provides an attractive advantage by reducing the risk of over-fitting comorbidity data in small datasets and limiting calculation requirements in large datasets. The use of summary comorbidity scores for the evaluation of comorbidity status was a more efficient method for predicting patients' survival than considering single comorbidities. This was a sound approach as the two indices were able to, "explore the comorbidity burden primarily by using a quantitative approach", with the CCI and the ECI chosen to evaluate comorbidity severity by weighting the comorbid conditions to assess clinical impact. (444)

The use of a diverse population including the geographic regions of Fife and Tayside to derive summary comorbidity scores represents another key strength of this study. Further, we used SMR01 data to refine patients' comorbidity status and used validated comorbidity summary scores. (441, 442) This study is an original attempt to validate any Elixhauser summary score using Scottish data, while the use of multiple measures to provide a robust comparison of model performance was another strong point.

CCI and ECI were used as the comparative comorbidity measures as they both allow for the use of a composite score of overall comorbidity classification. This is made up of the weighted score for each comorbid condition that has been identified as having an influence on the survival of cancer patients. The CCI has been validated to be applicable in the evaluation of head and neck cancer, (163) while there has been one previous attempt to validate the ECI within HNC (506) although this has been conducted in other diseases. (441, 443, 446, 493, 507, 508) The results revealed that CCI and ECI were useful indicators and should be widely applied in the evaluation of comorbidities.

Another main strength of this study is that we used evidence triangulation to measure SES, we used an area level measure, the Scottish SIMD quintiles and also the individual SIMD measures of income and education. Education was identified as a primary determinant for the development of cancers of the upper aerodigestive tract (551) therefore it would be logical that this factor would resultantly impact survival. (545). The chosen multiple imputation by chained equations method that was chosen uses conditional imputation models where one variable is imputed conditioning on other. This method may not be mutually consistent and consequently may not be reliable, (459) however, multiple imputation provides valid statistical inferences, because conducting the analysis with only complete cases would have biased the results of this study through the loss of a substantial number of cases from the analysis. (552)

There are also additional strengths in the study. Information on comorbidity was based on high quality administrative, SMR01 data hence it did not depend on the accuracy of the clinicians involved which would have left the data prone to bias, misclassifications and coding errors. However since comorbidity was derived independently prior to data linkage with information on the patient data, the misclassification could not occur. The data was provided through the HIC data team who ensured that the anonymised data received by the research team was matched to the patients' clinic data. It is unclear whether the HPV status of the patients in this cohort may have been useful as this information was not available due to lack of collection, but it could potentially have had important prognostic validity on the calculation of survival estimates. (42, 60, 231, 553)

To date, many studies have focused on cancer mortality; but in this instance this is the first time that a study has been carried out in Scotland, using data linkage of prognostic factors such as comorbidity and SES to estimate survival. Through the use of individual SIMD domains as well as an area based measure, we were able to conduct a comprehensive exploration of cancer survival risk

7.5. Weaknesses of the study

Firstly this work relied on administrative data, which are never complete or detailed enough to provide a clinically precise method for identifying comorbidities. The most important shortcoming of administrative data as is the case for this study is that it is not possible to identify when a condition became apparent. Complete SMR01 information has the ability to identify the timing of diagnoses as a way to differentiate between complications and comorbidities, however as we did not use timing of comorbidities, it is possible that some of the conditions we used to calculate comorbidity scores were in actual fact complications. In mitigation as per Feinstein's (1) definition of comorbidity we did not need to distinguish between either conditions present prior to or after the diagnosis of HNC. As there was no predetermined study commencement date given, there is a possibility of some case-mix differences due to treatment advances in HNC oncology, however the longer periods of follow up reported in the retrospective cohort analysis further enhances the long term prognostic risk prediction within this group of HNC patients. Although there was some potential of missing some comorbid conditions by using secondary care data, the use of the SMR data has been shown to be a key strength in recent papers. (548, 554, 555)

The focus for the systematic review was to determine how comorbidity and SES affected survival in combination. Only three studies were found that attempted to answer this question but in order to enhance the validity of the findings, studies that focused on both factors separately had to be included in the review. Unfortunately the comorbidity studies that were included in the systematic review did not report whether they treated SES as a confounder, therefore it is impossible to make any judgements on this, but it is possible that this may have affected the resultant pooled hazard ratio within the meta-analysis.

Secondly, the influence of lifestyle factors such as smoking and alcohol consumption was taken into account in order to determine their influence on outcomes, and these showed that heavy

drinking and excessive smoking had a negative impact on survival. The data on smoking and alcohol was based on self-report by patients hence it is possible that there was reporting bias in this information. (556) Recurrence-free survival was a key outcome measure identified at the time of devising this study; however, it could not be measured. This is because recurrence of HNC could only be ascertained in a few cases therefore a subgroup analysis was not possible. As pointed out by Sharabiani *et al* (557), 'risk adjustment modelling in comorbidity is essential', however the missing data may have limited the capacity to conduct accurate and robust risk prediction in this study. Another shortcoming was the influence of treatment on outcomes which could not be determined due to missing and/or incomplete data. The inclusion of outcomes data based on treatment type stratified by comorbidity status and SES would have enhanced the validity of the retrospective analysis by providing evidence to refute or substantiate whether these two prognostic factors were taken into account when clinical interventions were selected.

As the systematic review findings had shown that younger patients with severe comorbidity experienced premature mortality, the optimisation of survival based on the treatments selection would have shown whether older patients do indeed receive less invasive procedures while younger patients are given more aggressive treatments. As pointed out by Dronkers *et al* (558), patients are now partners in the clinical decision making process therefore an assessment of outcome based on chosen intervention requires a full understanding of not only the standard treatments, but also patient and clinician choice.

The reasons for treatment choice could be manifold with the main one for less invasive interventions being the debilitating effects of some curative treatments such as laryngectomy. Therefore, in spite of the recognition that an analysis of the treatment modalities would have provided meaningful evidence on the variation in age-related survival rates, choice of HNC treatment modalities are not straightforward and as such in the absence of rationale for choice of treatment, the usefulness of this data is diminished. The retrospective design introduced

information bias as data was obtained from routinely collected and medical record review when adding a survey would have provided rich data which could then account for patients' choice of treatment with the added benefit of checking whether their comorbidity and SES were linked. (16, 17, 499, 558-560)

This thesis demonstrated the inherent pitfalls of linked administrative data for research purposes. This was particularly the case for the Fife data which had missing data which required complex methods of missing data analysis as it provided the most cases compared to Tayside. This study had the advantage of using complex statistical methods to account for missing data as without these 199 cases would have been lost from the analysis. These methods enhanced the power of the study unlike other techniques for dealing with missing data such as list-wise or pair-wise deletion which would have reduced the statistical power of the study due to a reduction in patient numbers. The deleted may have held important information that could enhance the study findings and additionally the estimates would not be reliable as the data may have been missing completely at random. Multiple imputation methods have the added advantage that for each missing value the variability of the data is reduced and it also takes into account any variability due to sampling and variability due to the imputation itself.

All cause mortality and HNC specific mortality were the only outcome measures reported as the GRO death certification laws mean that a main cause of death and contributing causes are also given. For that reason, in order to minimise errors only the data given as the main cause of death were used to assign death from all causes and death from HNC. This study measured survival based on comorbidity and SES though amalgamation of patient data collected through disparate methods. Ideally the case note review which worked so well for the Tayside data should have been applied to the Fife data to allow for good quality data. The survival analysis was unable to employ methods of comorbidity assessment used in the prior systematic review as the ACE-27 index required more patient information that was readily available in the two data sources used.

The CCI and the ECI were used as the linked patient datasets had sufficient information to allow allocation of comorbidity status to each patient. CCI and ECI are two of the best known comorbidity indices, with the latter designed for use in databases. There is only partial overlap in the set of comorbidities that these two cover, and many diseases are not covered by either, which is why both were deemed ideal for this project. Although they were designed or at least suggested for general purpose use, there have been numerous attempts by researchers to adjust these indices for sets of diseases that are of particular importance to a specific patient group. (557) A further drawback is that these indices were originally used to predict 1-year mortality (CCI) or length of stay, hospital charges, and in-hospital death (Elixhauser), whereas other outcomes such as 5 year or even longer-term survival which are of interest in this thesis would have been difficult to accurately predict.

Ghali et *al* (561) refuted the utility of summary comorbidity indices such as CCI and ECI stating that the prognostic ability of summary measures created using one's own data were superior to that of measures derived using published algorithms which they were able to prove within a sample of patients undergoing coronary artery bypass graft surgery. These findings were also confirmed by Schneeweiss and Maclure (562) in a cohort of patients receiving angiotensin-converting enzyme inhibitors or calcium-channel blockers by suggesting that confounding which using CCI and ECI without deriving study specific weights would remain uncontrolled resulting in unreliable findings which was backed up by Hansen who suggested that the summary measures, or prognostic scores as he terms them, be estimated using a researcher's own data. In contrast Austin *et al* (448) presented the argument for, "the general theoretical justification for prognostic scores such as CCI by demonstrating that comorbidity summary measures can have properties similar to propensity scores thereby removing confounding in observational studies".

Another potential drawback of using linked health data rendered some planned analysis redundant due to missing data and incomplete information. The lack of consistency and accuracy

of key variable information such as gender, HNC sub type, age, status (i.e. dead or alive), smoking status and alcohol consumption meant that some key analyses could only be conducted after complex analysis, multiple imputation method. This reduced the generalisability of the study findings. These variables would have provided meaningful prognostic indicators for survival and disease recurrence.

The prognostic utility of comorbidity on head and neck cancer may be determined by factors such as disease stage but this could not be elicited fully due to missing data. In spite of these limitations, this study was able to confirm that both comorbidity and SES independently and in combination affected the survival outcomes of HNC patients. As there is no scope for the prevention of comorbidity or deprivation in the context of HNC care and treatment, oncologists need to develop clinical practice guidelines (CPGs) that take account of these two factors as much as possible. It is acknowledged that clinical practice guidelines may not fully facilitate accurate decision making processes, due to the complexity of HNC patients who have comorbidities.

One of the main limitations arising from this thesis is the feasibility of comorbidity data collection in creating the comorbidity summary score. It would have been ideal to extract the ICD-9 and ICD-10 codes into meaningful comorbidity conditions using predefined statistical data mining syntax, however there was no evidence of these being available for use in SPSS. This meant that manual methods of obtaining the relevant comorbidity conditions included in both the CCI and ECI. This method had potential shortcomings due to coding errors but this was minimised through the use of predetermined codes for comorbidity extraction. (438, 439)

This thesis presents for the first time linkage of HNC incidence data from Fife and Tayside providing a large cohort and number of primary tumours followed up for several years. Finally, the confirmation of the HNC population through the cancer registry and SMR01 records demonstrates evidence of high data quality and information triangulation.

7.6. Implications

This study confirmed the multiplicative prognostic importance of both comorbidity and SES. It is clear from the survival analysis that being deprived and having severe comorbidity increases the risk of mortality. As both factors are important determinants of HNC survival, it is imperative that oncologists mitigate for their effect not only on stage at diagnosis, but survival and subsequently long term quality of life. A clear management plan to optimise treatments needs to be tailored to each patient taking into account patient factors i.e. comorbidity and SES amongst the patient-related factors and for the tumour factors such TNM and disease stage. As recommended by Sarfati (105) a risk profile of a patient is easily created by taking note of the patient and tumour factors, and although no specific tool was recommended ECI was retained due its superiority over the CCI. It is feasible that HNC patients can have proper risk stratified care based on their comorbidity status and SES as this will take account of the threat posed by these patient-related alongside tumour factors such as disease stage and type of HNC. (312, 563-565)

Hence from the findings it may be possible to create a short comorbidity index that would focus on factors of which are known to predict outcome using the Elixhauser index and additional comorbidities such as smoking >20 cigarettes/day and level of education using a self-administered questionnaire such as that proposed by Molto and Dougados (566). In case of issues around self-reporting bias, the healthcare staff could collect the comorbidity information although with workload pressure this may be difficult. It would be possible to overcome this challenge by creating a comorbidity index that would be easy to apply within the oncology setting. A short index (akin to the widely used Mini Mental state Exam) which includes a small number of comorbidities may work well and as pointed out by Marventano *et al*, (444) the proposed index should focus on conditions known to affect HNC so as to fully assess their impact on survival. If the data are available then using an already validated tool such as the WUHNCI to

measure comorbidity would also be a great method of collecting comorbidity data which feeds into the personalised medicine approach advocated in this study.

It is acknowledged that the retrospective cohort study methods had a shortcoming, i.e. that the individual SES domains are based on area level SES measure (SIMD) hence these individual domains may not reflect individual SES accurately i.e. an 'ecological fallacy' may occur. SIMD uses ecological data this allows for the drawing of inferences which may not directly applicable to the individual, (567) Area rather than individual measures of SES such as SIMD are created for the smallest available administrative unit, out of necessity, are increasingly used worldwide to measure effects of SES on health outcomes and to plan services and may be used as surrogates for individual social indicators. This justifies the use of the SIMD rendering the results of this study clinically important and the chance of misclassification of SES very small. (282, 568-570) This is a novel presentation of time data linkage of administrative data on HNC incidence, comorbidity and SES which provided a large cohort, linked to SMR01, Cancer Registry and GRO death data.

When interactions between age and SES that were found in an earlier systematic review were tested, only age, i.e. being younger was shown to increase the hazard of mortality. Our findings on the inter-relationship between area deprivation and education show the synergistic effect of area and individual SES measured by education and which is consistent with others focusing on cancer. Sharpe *et al* (543) reported an inter-relationship between area levels of deprivation and education which has congruence with our study. Given these cancers are largely driven by smoking and alcohol behaviours, which are both more prevalent among the more deprived implies that social and cultural aspects of SES are important in uptake and continuation of smoking and alcohol consumption. Education level captures the impact of socioeconomic and cultural circumstances at an early age when adopting the habits that predispose to the

development of HNC. In addition, the differences between the sexes in the smoking epidemic are likely to explain the mitigating effects identified.

Cancer survival as determined by SES has received attention from researchers previously with SES defined using income level data or level of education while others have employed proxy measures such as occupation and particularly in America health insurance status. (309) (540, 546) Survival is influenced by a range of individual and tumour factors such as SES and comorbidity. Patients of low SES and of more advanced age have a higher likelihood of having comorbidity this may be due to risky lifestyle behaviours such as smoking and drinking. Brusselaers *et al* (486) found that higher education levels had improved survival compared to less well educated in oesophageal cancer.

With the classic risk factors of alcohol and smoking in addition to HPV- related incidence, there is also the continuing shift in population structures with more people surviving longer, comorbidities are becoming more common alongside cancer. Also the number, type and severity of these coexistent diseases has been said to increase with age which consequently affects survival. (146) Yung *et al* (150) found that comorbidity had an independent prognostic effect on HNC survival and that relative risk of death increased two times due to advanced comorbidity. (380)

Specific comorbidity such as cardiac, respiratory, cardiovascular, cerebro-vascular, dementia, renal, hepatic, weight/nutrition and previous surgery/radiotherapy/chemotherapy are of particular importance in HNC based on research conducted by Peake. (151) Therefore it is not difficult to assume that deaths will become more frequently attributed to comorbidity compared to index diseases such as HNC. The Scottish Head and Neck Cancer Audit found that deprivation survival relationship was largely explained by WHO performance status. However there are distinct conceptual differences between comorbidity and performance status. The WHO Performance status differs from comorbidity as it seeks to ascertain how well a patient is able to

carry out normal activities while living with cancer. It does not provide a method of measuring co-existing conditions i.e. comorbidity. It is particularly useful for evaluating treatment response, whether and how the cancer is progressing, ascertaining the patient's tolerance of cancer treatments through the assessment of physical health. It can also be used as a method for selecting clinical trial participants. The only similarity to comorbidity assessment is the ability to estimate prognosis.

To date, many studies have focused on cancer mortality; here for the first time in Scotland, multiple individual SES metrics were used to explore HNC mortality risk. Comorbidity is frequent in HNC patients due to the aetiological factors, smoking and alcohol consumption which have a negative impact on survival, therefore assessment of comorbidity is of great importance, both in order to treat/optimize patient's health before treatment commences and also in order to be able to stratify/control for comorbidity in randomized trials for HNC therapeutic interventions. A key strength from this project is the methodological quality assessment tool as it carries a lot of potential for both use and application. It could be used to do quality assessment of papers focused on diseases other than HNC. It is easily adaptable to any condition as the quality assessment questions help to identify methodological rigour in a primary research paper that focuses on survival. The utility of application of this tool in other areas is immense as it really focuses on papers that investigate time to an event and an example could be weight management in renal disease.

The accuracy of the information provided through the linkage of health data enabled the assessment of demographic patterns in the distribution of comorbidity and SES within the HNC population in Fife and Tayside. This information is critical for adaptation and enhancement of oncology services in order to mitigate the risk of poor outcomes in HNC patients. Creating collection of additional information on comorbidity that can be assessed by cancer registry staff (such as the incorporation of comorbidity advocated by the National Cancer Intelligence Network

(151, 152) will also be useful, as will information on how patients with HNC are clinically managed and the treatment adjustment dependent on patient factors and tumour characteristics. Collectively, these data will help clinicians and policymakers to identify any gaps in the care of patients with HNC, alongside comorbidity and low SES. This will mean that clinicians will be able to organise care delivery to optimally address identified gaps.

The main issue that arose in this study is that patients need to have their individual circumstances addressed. It is necessary as part of the holistic approach to care and treatment of oncology patients in order to tailor the treatments based on both tumour and host factors. HNC patients who have severe comorbidity and are deprived have higher likelihood of premature mortality, but careful monitoring of the interplay between host and tumour factors may improve chances of survival, while reducing the likelihood of HNC recurrence. This study makes the case for proper assessment of the influence of comorbidity and SES on head and neck cancer prognosis.

7.7. Chapter summary

This chapter reviewed the results of the survival analysis and how these could be applied within clinical practice. The shortcomings and the strengths of the survival analysis were also discussed, and these results were placed within the context of congruence with prior work (the systematic review in Chapter 2) carried out as part of the thesis. The final chapter will explain what the findings of this thesis mean and give indication of further work that could be done to fully explore the implications of comorbidity and deprivation within HNC oncology. It will make sense of what the project found by comparing and contrasting the systematic review and the retrospective cohort study. It will review whether the research questions have been answered fully. Any shortcomings at this point will be highlighted and any directions for future work will be given. What this thesis adds to the body of evidence on the effect of comorbidity and deprivation on HNC survival will also be presented in Chapter 8.

Chapter 8

8.1. Conclusions

8.1.1. Chapter summary

This chapter will provide a brief summary of the results of the thesis. The findings from both the systematic review and the data linkage study will be reviewed against the aims and objectives of the thesis. Any lessons that were learned during the conduct of this thesis will also be discussed. A discussion on the implications of the findings will be conducted as well as recommendations for future research studies that may contribute to unravelling the individual contribution of deprivation and comorbidity in HNC survival. This would allow for an enhanced understanding of whether this contribution is multiplicative or independent. In addition any recommendations on future research will be given, prior to a conclusion on the project results presented in this thesis.

8.2. Summary of findings

The poor survival of HNC patients who have comorbidities and from deprived backgrounds remains a major issue for clinicians working in this field of oncology. The work reported in this thesis used robust methods to explore whether comorbidity and deprivation had an influence on the stage at presentation and survival of patients with head and neck cancer.

The original objectives for the project are depicted below:

Aim: The project aimed to answer a number of specific research questions:

1. To investigate the roles and interrelationship between comorbidity and deprivation on the survival of HNC patients.

2. To investigate whether there are differences in HNC presentation based on comorbidity and deprivation.

3. To ascertain whether patients from deprived backgrounds with comorbidity present with more advanced cancers.

This thesis began with a systematic review to confirm whether there was prior empirical evidence that evaluated the effect of both comorbidity and SES in HNC patients. The systematic review found three studies that focused on both factors. All three found that severity of comorbidity was associated with poor survival, but in terms of SES only two out of three studies found a socioeconomic gradient for survival. Although there were heterogenous methods used in the measurement of either factor, the systematic review was able to establish a connection between both comorbidity and SES on survival in HNC.

As a follow up to the systematic review, the next step was an examination of a cohort of patients with HNC to describe SES and comorbidity on diagnosis and any subsequent effect on mortality. This study provided evidence of mortality risk dependent on comorbidity measured using the ECI, and SES measured using the SIMD income and education domains.

8.3. Reflection on this work

It is apparent from the results presented in this thesis, that there is some interaction and influence of both comorbidity and SES on HNC outcomes. This thesis was able to triangulate the findings of the systematic review with those of the survival analysis using Cox proportional hazards regression methods. Income and education were found to have an impact on survival in the systematic review, and this relationship was confirmed in the survival analysis with definitive evidence of statistical significance. This makes the case for a shift in focus from the use of time proven prognostic factors such as the TNM classification alone. The research conducted here has

also demonstrated the prognostic importance of social health determinants such as SES within oncology. (166)

Another point to note is that research has pointed to the importance of performance status as an additional marker for patient complexity. The WHO Performance status differs from comorbidity as it seeks to ascertain how well a patient is able to carry out normal activities while living with cancer. It does not provide a method of measuring co-existing conditions i.e. comorbidity but it is particularly useful for evaluating treatment response, whether and how HNC is progressing, ascertaining the patient's tolerance of cancer treatments through the assessment of physical health. It can also be used as a method for selecting clinical trial participants. The only similarity to comorbidity assessment is the ability to estimate prognosis.

This is of particular relevance as the Scottish Head and Neck Cancer Audit found that the deprivation survival relationship was largely explained by WHO performance status although this is not an objective of this project. In essence future work should also take the patient's performance status alongside deprivation and comorbidity in order to have a complete understanding of the patient-related factors in order to conduct a thorough assessment and provide interventions that are personalised to each patient.

This project has been able to identify the intrinsic complexities of relying on area measures of deprivation and counts of comorbidity. Nevertheless this study was able to mitigate for these in order to assess risk of mortality by using complementary measures of SES, i.e. SIMD alongside income and education domains and for comorbidity; by using two weighted indices of comorbidity measurement. This interlinking of comorbidity and SES poses particular challenges as there are changes in cancer risk due to aging populations which not only represents the complex, and multifaceted challenge of attempting to improve survival in HNC patients. This complexity will take time to lessen in the face of treatment advances and improved patient assessment and tailored treatment regimens.

In conclusion, the different and independent SES and comorbidity measures have been shown to be associated with worse outcomes in patients with HNC. Of interest is that the different measures of comorbidity (ECI and CCI) had different effects on survival with ECI being shown to be slightly better at calculating mortality risk. Additionally only the SIMD income and education domains had the superior ability in capturing hazards of death despite the SIMD quintiles and the income and education domains being based on the same area level measure of deprivation. The inherent difficulties of measuring SES and comorbidity accurately go some way towards a reflection of the complexity and multifaceted nature of both comorbidity and SES.

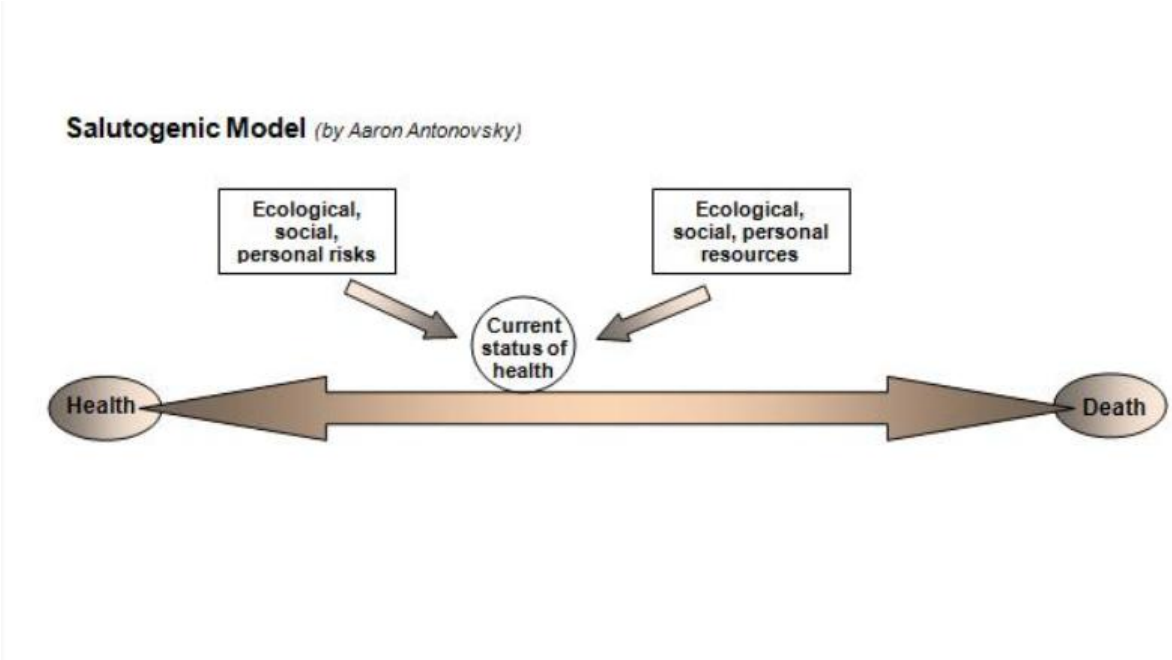
8.4. Future work

Although both the systematic review and the retrospective cohort study achieved their aims, there may be scope for further work in this area of prognostication. As described by Munro and Bentley (145) the interrelationships between comorbidity, deprivation and outcome in a group of patients are complex. There is the possibility that in order to investigate any interrelationship between comorbidity and deprivation it is helpful to have a cohort of patients in whom decisions concerning assessment and clinical management have been uniform and consistent over time. Using administrative data linked to medical records is not enough, there is need for epidemiological and clinical studies to unravel the survival disadvantage. To this end clinical cohorts could be nested within larger registry based studies. All patients can be assessed prospectively and their full clinical history and type of HNC and staging information confirmed through pathological examination entered into electronic patient records. The patients' care would follow the Clinical Practice Guidelines (CPGs) recommended for HNC; however their unique comorbidities and SES would be taken into account. Comorbidity would ideally be assessed using the Washington University Head and Neck Cancer Index (WUHNCI) but as the ECI (441) has been used in this project, that alongside SES using the SIMD income and education domains would both be ideal as both methods have been validated in this thesis. If this work

could be done in the two regions of Fife and Tayside and expanded to other centres such as Edinburgh and Glasgow, this could provide validation of modification to HNC care and treatment with the objective of improving survival outcomes. In spite of healthcare advances, inequalities in health still exist and it is envisaged that factors like SES will continue to have a detrimental effect on survival.

The project was unable to unravel how both deprivation and comorbidity interrelate. It was clear however, that this review could have elicited more meaningful findings, had the inclusion of a social cognition model been taken into account. The rationale for this is that this project relied on measures of comorbidity and deprivation which have a myriad of shortcomings. The fact that an individual is defined as being deprived using the SIMD domains does not reflect an HNC patient's self perception of social standing. Social standing is not permanent as individual circumstances may change. SIMD uses census data which is only available every 10 years and therefore the SES of a particular individual may change during that time. In terms of comorbidity, there is some utility of summary comorbidity indices such as CCI and ECI but these indices do not include all additional conditions therefore bias is a possibility here. Comorbidity indices have utility as both clinical tools and for epidemiological and/or research studies as most can be easily or readily scored or computed within the clinic. With improved understanding of the mechanisms of comorbidity, the additional data will be useful within health services research particularly as part of a personalised holistic approach. The variability of comorbidity and deprivation shown here requires further exploration. This is best illustrated using the Salutogenic model (Figure 50) which considers the issue of health creation i.e. improved health suggesting a continuum of influences that are essential to individual health behaviours and other extrinsic factors that ultimately lead to death in HNC patients.

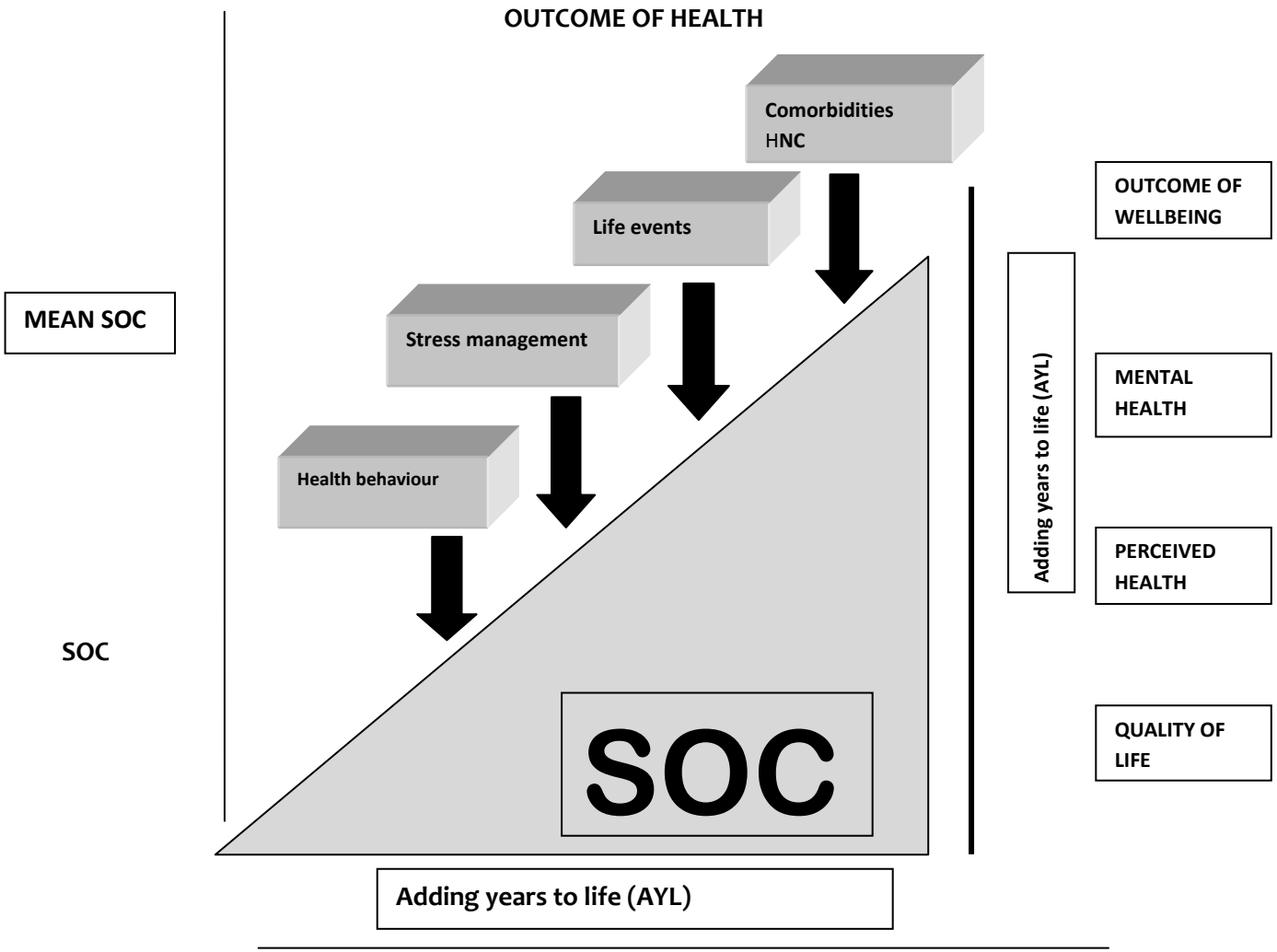
Figure 50 Salutogenic model



The Salutogenic Model Adapted from International Public Health Partnership (571)

This model shares similar factors to Dahlgren and Whitehead's social determinants of health model (76) and provides a mechanism of unpacking the interwoven complexity of the elative contribution of comorbidity and deprivation in HNC presentation and survival. Figure 45 shows exactly where within the health continuum, comorbidity and SES are found. Granted the indices of comorbidity and SES have applications for the analysis of the data, but a fuller understanding of patient factors go a long way into the application of personalised treatment and care. This is where the Salutogenic model's sense of coherence comes under consideration. If Figure 51 is used as an aid into developing an holistic approach to the HNC patient, this will contribute to the richness of the results from this data.

Figure 51 Salutogenic model – Sense of Coherence



This model attempts to elicit what keep people healthy by asking a series of questions which all go towards the underlying question, 'why do some people, despite stressful situations in their lives, manage to stay healthy and others do not?' (572) This is especially important as not all the people who smoke and drink excessively are known to develop HNC despite both factors having a known multiplicative contribution to carcinogenesis. The sense of coherence is measured using

An additional method to further validate this would be to use pharmacy based comorbidity evaluation methods such as that proposed by Sarfati *et al* (83) in order to explore the issue of polypharmacy and pharmacokinetics in determining how comorbidity treatments impact cancer therapies and efficacy of same.

This thesis addressed the quite complex interplay between SES, comorbidity, stage at diagnosis, and access to care in head and neck cancer, and these factors' ultimate impact on survival. We found that SES, comorbidity, stage at diagnosis, access to care, and survival are all potentially causally related. From the findings of this thesis, as future direction for this area of HNC prognostication we hypothesise the causal direction as: lower SES leads to poor access to healthcare, which in turn leads to both advanced stage at diagnosis as well as increased comorbidity, which then both impact survival; therefore it would make sense conduct prospective cohort analysis using the salutogenic model. This would consider how health beliefs such as perceived health in the salutogenic sense of coherence (398, 572) can contribute to determining outcomes alongside other external factors in HNC patients. This is of particular importance as the salutogenic theory has been described, 'as a position on a health ease/dis-ease continuum and the movement in the direction towards the health end'. (572, 573) As shown in chapter 2the salutogenic model has a role to play in disentangling exactly how comorbidity and deprivation (low SES) contribute to poor survival outcomes in HNC patients.

8.5. Final thoughts

In this thesis both comorbidity and SES were important indicators of survival in HNC. When assessing the influence of comorbidity and SES alongside other known prognostic factors such as smoking, alcohol, disease stage, HNC type and age, both factors were shown to have a significant independent effect on overall survival. As the world population ages there will be more elderly HNC patients and many of these will have comorbidity at the time of diagnosis. These results support the fact that comorbidities should be assessed in prognostic staging of patients and comorbidity should be treated in order to optimize and gain a survival benefit from treatment.

There is evidence showing that comorbidity and SES are important factors influencing the survival of HNC patients in the developed world. However, to the best of our knowledge, no studies have reported the influence of comorbidities and deprivation on the prognosis of HNC in Scotland. The current study is the first to confirm that comorbidities and SES were both interrelated and independent factors affecting the prognosis of overall and disease free survival of patients with HNC. This study has been able to demonstrate that the value of comorbidity and SES in HNC survival was comparable to that of clinical stages. In conclusion, our findings suggest that administrative databases may be a useful tool for surveillance of the prognostic importance of comorbidity and SES. . However, it is striking that routinely collected administrative health data do not often include information on measures of comorbidity and SES. It appears as if it's necessary to reconsider the potential benefits of tailoring treatment to the patient at the point of cancer care delivery.

References

1. Feinstein RA. The pre-therapeutic classification of co-morbidity in chronic disease. Journal of Chronic Diseases. 1970;23:455-68.
2. MacArdle O, Mahony D. Oncology: An illustrated colour text. Edinburgh: Churchill Livingstone Elsevier; 2008.
3. Alvarenga LM, Ruiz MT, Pavarino-Bertelli EC, Ruback MJ, Maniglia JV, Goloni-Bertollo M. Epidemiologic evaluation of head and neck patients in a university hospital of Northwestern São Paulo State. Braz J Otorhinolaryngol. 2008;74(1):68-73.
4. Scottish Government. Cancer Scenarios. Edinburgh: Scottish Government; 2010.
5. MacMillan Cancer Support. Head and neck cancers. MacMillan Cancer Support; 2010 [cited 2010 12 November]; Available from: http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Headneck/Headneckcancers.aspx.
6. National Cancer Insitute. Factsheet: Head and Neck Cancer. National Cancer Insitute; 2010 [cited 2010 10 December]; Available from: http://www.cancer.gov/cancertopics/factsheet/Sites-Types/head-and-neck.
7. World Health Organisation. International Statistical Classification of Diseases and Related Health Problems10th Revision. 2010 [cited 2010 10 October]; 10th:[Available from: http://www.who.int/classifications/icd/en/.
8. National Institute for Clinical Excellence. Improving outcomes in head and neck cancers: The manual. NICE; 2004 [cited 2011 13 November]; Available from: http://www.nice.org.uk/nicemedia/pdf/csghn_themanual.pdf.
9. Boyle P, Levin B, editors. The World Cancer Report. Lyon International Agency for Research on Cancer; 2008.
10. Peters TTA, Van Dijk BAC, Roodenburg JLN, Van Der Laan BFAM, Halmos GB. Relation between age, comorbidity and complications in patients undergoing major surgery for head and neck cancer. Annals of Surgical Oncology. 2014;21(3):963-70.
11. Boeje CR. Impact of comorbidity on treatment outcome in head and neck squamous cell carcinoma - A systematic review. Radiotherapy and Oncology. 2014;110(1):81-90.
12. Maggiore RJ, Gross CP, Hurria A. Polypharmacy in Older Adults with Cancer. The Oncologist. 2010 May 1, 2010;15(5):507-22.
13. Bretherton A, Day L. Polypharmacy and older people. Nursing Times. 2003;99(17):54.
14. Jorgensen TL, Hallas J, Land LH, Herrstedt J. Comorbidity and polypharmacy in elderly cancer patients: the significance on treatment outcome and tolerance. Journal of Geriatric Oncology. 2010;1(2):87-102.
15. Borggreven PA, Kuik DJ, Quak JJ, et al. Comorbid condition as a prognostic factor for complications in major surgery of the oral cavity and oropharynx with microvascular soft tissue reconstruction Head Neck. 2003;25:808-15.
16. Derks W, de Leeuw JRJ, Hordijk GJ, Winnubst JAM. Reasons for non-standard treatment in elderly patients with advanced head and neck cancer. European Archives of Oto-Rhino-Laryngology. 2005 Jan;262(1):21-6.
17. Derks W, De Leeuw RJ, Hordijk GJ. Elderly patients with head and neck cancer: The influence of comorbidity on choice of therapy, complication rate, and survival. Current Opinion in Otolaryngology and Head and Neck Surgery. 2005;13(2):92-6.
18. Peters TTA, van der Laan BFAM, Plaat BEC, Wedman J, Langendijk JA, Halmos GB. The impact of comorbidity on treatment-related side effects in older patients with laryngeal cancer. Oral Oncology. 2011;47(1):56-61.
19. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: A Cancer Journal for Clinicians. 2011;61(2):69-90.

20. Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics, 2002. CA: A Cancer Journal for Clinicians. 2005;55(2):74-108.
21. Duvvuri U, Myers JN. In Brief: Cancer of the head and neck is the sixth most common cancer worldwide. Current Problems in Surgery. 2009;46(2):114-7.
22. ISD Scotland. Cancer incidence in Scotland (2013). Edinburgh: ISD Scotland; 2015 [cited 2015 25 May]; Available from: https://isdscotland.scot.nhs.uk/Health-Topics/Cancer/Publications/2015-04-28/2015-04-28-Cancer-Incidence-Report.pdf?70922487975.
23. Warnakulasuriya S. Living with oral cancer: epidemiology with particular reference to prevalence and lifestyle changes that influence survival. Oral Oncol. 2010;46:407-10.
24. Macfarlane G, P Boyle, C Scully. Rising mortality from cancer of the tongue in young Scottish males. The Lancet. 1987;2:912.
25. Neal AJ PH. Clinical oncology: basic principles and practice. London: Hodder Arnold; 2009.
26. Information Services Division. Head and neck cancer. Edinburgh: ISD; 2012 [cited 2012 17 May]; Available from: http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Head-and-Neck/.
27. Scheich L. HPV related cancer: an equal opportunity danger. Nursing. 2010;40(10):22-8.
28. Lassen P. The role of Human papillomavirus in head and neck cancer and the impact on radiotherapy outcome. Radiotherapy and Oncology. 2010;95(3):371-80.
29. Boscolo-Rizzo P, Del Mistro A, Bussu F, Lupato V, Baboci L, Almadori G, et al. New insights into human papillomavirus-associated head and neck squamous cell carcinoma. Acta Otorhinolaryngologica Italica. 2013;33:77-87.
30. Genden E, Sambur I, de Almeida J, Posner M, Rinaldo A, Rodrigo J, et al. Human papillomavirus and oropharyngeal squamous cell carcinoma: what the clinician should know. European Archives of Oto-Rhino-Laryngology. 2013 2013/02/01;270(2):405-16.
31. Dahlstrand H, Nasman A, Romanitan M, Lindquist D, Ramqvist T, Dalianis T. Human Papillomavirus Accounts both for Increased Incidence and Better Prognosis in Tonsillar Cancer. Anticancer Research. 2008 March 1, 2008;28(2B):1133-8.
32. Dayyani F, Etzel CJ, Liu M, Ho C-H, Lippman SM, Tsao AS. Meta-analysis of the impact of human papillomavirus (HPV) on cancer risk and overall survival in head and neck squamous cell carcinomas (HNSCC). Head & Neck Oncology. 2010;2:15-.
33. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res. 1988;48:3282.
34. Zygogianni A, Kyrgias G, Karakitsos P, Psyrri A, Kouvaris J, Kelekis N, et al. Oral squamous cell cancer: early detection and the role of alcohol and smoking. Head & Neck Oncology. 2011;3(1):2.
35. Talamini R, Bosetti C, La Vecchia C, Dal Maso L, Levi F, Bidoli E, et al. Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. Cancer Causes Control. 2002;13:957-64.
36. Agrawal N, Frederick MJ, Pickering CR, Bettegowda C, Chang K, Li RJ, et al. Exome Sequencing of Head and Neck Squamous Cell Carcinoma Reveals Inactivating Mutations in NOTCH1. Science. 2011 August 26, 2011;333(6046):1154-7.
37. Rothman KJ, Cann CI, Flanders D, et al. Epidemiology of laryngeal cancer. Epidemiol Rev. 1980;2:195.
38. Boffetta P, Mashberg A, Winkelman R, Garfinkel L. Carcinogenic effect of tobacco smoking and alcohol drinking on anatomic sites of the oral cavity and oropharynx. Int J Cancer. 1992;52(4):530-33.
39. La Vecchia C, Tavani A, Franceschi S, Levi F, Corrao G, Negri E. Epidemiology and prevention of oral cancer. Oral Oncol. 1997;33(5):502-12.
40. Swerdlow AJ, Marmot MJ, Grulich AG, Head J. Cancer mortality in Indian and British ethnic immigrants from the Indian subcontinent to England and Wales. Br J Cancer. 1995;72:1312-19.
41. Johnson NW, Warnakulasuriya KAAS. Epidemiology and aetiology of oral cancer in the United Kingdom. Community Oral Health. 1993;10:13-24.

42. Goon P, Stanley M, Ebmeyer J, Steinstrasser L, Upile T, Jerjes W, et al. HPV & head and neck cancer: a descriptive update. Head & Neck Oncology. 2009;1(1):36.
43. Zhang Z. Marijuana use and increased risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol Biomarkers Prev. 1999;8(12):1071 - 8.
44. Berthiller J, Lee Y-cA, Boffetta P, Wei Q, Sturgis EM, Greenland S, et al. Marijuana Smoking and the Risk of Head and Neck Cancer: Pooled Analysis in the INHANCE Consortium. Cancer Epidemiology Biomarkers & Prevention. 2009 May 1, 2009;18(5):1544-51.
45. Hashibe M, Straif K, Tashkin DP, Morgenstern H, Greenland S, Zhang Z-F. Epidemiologic review of marijuana use and cancer risk. Alcohol. 2005;35(3):265-75.
46. NHS Centre for Reviews and Dissemination. Effective health care: Management of Head and Neck Cancers. York: NHS Centre for Reviews and Dissemination; 2004 [cited 2011 12 November 2010]; Available from: http://www.york.ac.uk/inst/crd/EHC/ehc85.pdf.
47. Wunsch F. The epidemiology of laryngeal cancer in Brazil. Sao Paulo Medical Journal. 2004;122(5):188-94.
48. Ferlay J, Bray F, Pisani P, Parkin D, editors. Globocan 2002: Cancer incidence and mortality worldwide. Lyon: IARC; 2004.
49. Gillespie M, S Rubinchik, B Hoel, N Sutkowski. Human papillomavirus and oropharyngeal cancer: what you need to know in 2009. Current Treatment Options in Oncology. 2009;10(5-6):296-307.
50. Mehanna H, T Jones, V Gregoire, K Kian Ang. Oropharyngeal carcinoma related to human papillomavirus. BMJ. 2010;340(1439).
51. Mehanna H, CML West, C Nutting, V Paleri. Head and neck cancer Part2: Treatment and prognostic factors. BMJ. 2010;341(4690):721-25.
52. Licitra L, F Perrone, P Bossi, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. J Clin Oncol. 2006;24(36):5630-36.
53. The Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. [Article]. 2015;517(7536):576-82.
54. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide Trends in Incidence Rates for Oral Cavity and Oropharyngeal Cancers. Journal of Clinical Oncology. 2013 November 18, 2013.
55. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence Trends for Human Papillomavirus–Related and –Unrelated Oral Squamous Cell Carcinomas in the United States. Journal of Clinical Oncology. 2008 February 1, 2008;26(4):612-9.
56. IARC. Monographs on the evaluation of carcinogenic risks to humans: Human papillomaviruses. Lyon: International Agency for Research on Cancer2007.
57. Franceschi S, Muñoz N, Bosch SF, Snijders SJ, WalboomersJM. Human papillomavirus and cancers of the upper aerodigestive tract: a review of epidemiological and experimental evidence. Cancer Epidemiol Biomarkers Prev. 1996;5(7):567-75.
58. Hall SF, Groome PA, Irish J, O'Sullivan B. The natural history of patients with squamous cell carcinoma of the hypopharynx. Laryngoscope. 2008 Aug;118(8):1362-71.
59. Kreimer AR, Bhatia RK, Messeguer AL, González P, Herrero R, Giuliano AR. Oral Human Papillomavirus in Healthy Individuals: A Systematic Review of the Literature. Sexually Transmitted Diseases. 2010;37(6):386-91 10.1097/OLQ.0b013e3181c94a3b.
60. Lill C, Kornek G, Bachtiary B, Selzer E, Schopper C, Mittlboeck M, et al. Survival of patients with HPV-positive oropharyngeal cancer after radiochemotherapy is significantly enhanced. Wien Klin Wochenschr. 2011 Apr;123(7-8):215-21.
61. Parkin D, Bray F. Chapter 2: The burden of HPV-related cancers. Vaccine. 2006;24(Suppl 3):11 - 25.
62. Termine N. HPV in oral squamous cell carcinoma vs head and neck squamous cell carcinoma biopsies: a meta-analysis (1988-2007). Ann Oncol. 2008;19(10):1681 - 90.

63. Weinberger PM, Merkley MA, Khichi SS, Lee JR, Psyrri A, Jackson LL, et al. Human papillomavirus-active head and neck cancer and ethnic health disparities. Laryngoscope. 2010 Aug;120(8):1531-7.
64. Genden E, Varvares M, editors. Head and neck cancer: an evidence based team approach. New York: Thieme; 2010.
65. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical and molecular entity. Head & Neck Oncology. 2004;31(6):744-54.
66. Gillison M. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst. 2000;92(9):709 - 20.
67. Weinberger PM, Z Yu, BG Haffy, et al. Molecular classification identifies a subset of human papillomavirus- associated oropharyngeal cancers with favourable prognosis. J Clin Oncol. 2006;24(5):736-47.
68. Schwartz S. Human papillomavirus infection and survival in oral squamous cell cancer: a population-based study. Otolaryngol Head Neck Surg. 2001;125(1):1 - 9.
69. Fakhry C. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100(4):261 - 9.
70. National Cancer Intelligence Network. One, five and ten yea cancer prevalence by Cancer Network: National Cancer Intelligence Network2006.
71. Feber T. Head and neck oncology nursing. London: Whurr Publishers Ltd; 2000.
72. Galdas PM, Cheater F, Marshall P. Men and health help-seeking behaviour: literature review. Journal of Advanced Nursing. 2005;49(6):616-23.
73. Hart CL, DJ Hole, CR Gillis, G davey Smith, GCM Watt, VM Hawthorne. Social class differences in lung cancer mortality: risk factor explanations using two Scottish cohort studies. International Journal of Epidemiology. 2001;30(2):268-74.
74. Bungay H. Cancer and Health Policy: The Postcode Lottery of Care. Social Policy & Administration. 2005;39(1):35-48.
75. Logemann J, B Roa Pauloski, A Rademaker, L Colangelo. Speech and swallowing rehabilitation for head and neck cancer patients. Oncology. 1997;11(5).
76. Dahlgren G, Whitehead M. Policies and strategies to promote social equity in health. Stockholm: Institute for future studies; 1991.
77. Golusinski W, Wasniewska E, Kaczmarek J, Kedzia D, Wrobel M, Malinowska B. Patients under 45 years of age "young adults" with head and neck squamous cell carcinoma. Retrospective, multivariable analysis--preliminary report Otolaryngol Pol. 2003;57(2):185-9.
78. Karin Silver K, Bauld L, Grant L, Warnakulasuriya S, Day R. The Experiences of Younger Oral Cancer Patients in Scotland: From Self-diagnosis to Treatment. In: Clyde NGGa, editor. Glasgow: NHS Greater Glasgow and Clyde; 2008.
79. Lacy PD, Piccirillo JF, Merritt MG, Zequeira MR. Head and neck squamous cell carcinoma: Better to be young. Otolaryngology - Head and Neck Surgery. 2000;122(2):253-8.
80. Lalami Y, De Castro G J, Bernard-MartyC, Awada A. Management of head and neck cancer in elderly patients. Drugs Aging. 2009;26(7):571-83.
81. Foot C, Harrison T. How to improve cancer survival: Explaining England's relatively poor rates: The King's Fund, Cancer Research UK2011.
82. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining Comorbidity: Implications for Understanding Health and Health Services. The Annals of Family Medicine. 2009 July 1, 2009;7(4):357-63.
83. Sarfati D, Gurney J, Stanley J, Lim BT, McSherry C. Development of a pharmacy-based comorbidity index for patients with cancer. Medical Care. 2014;52(7):586-93.
84. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, et al. Diabetes and Cardiovascular Disease: A Statement for Healthcare Professionals From the American Heart Association. Circulation. 1999 September 7, 1999;100(10):1134-46.

85. Berkson J. Limitations of the application of 4-fold tables to hospital data. Biomet Bull. 1946;2:47–53.
86. Fried LP, L Ferrucci, J Darer, JD Williamson, G Anderson. Untangling the concepts of disability, frailty and comorbidity: implications for improved targeting and care. J Gerentol A Bio Sci Med Sci. 2004;59:255-63.
87. Hall SF. A user's guide to selecting a comorbidity index for clinical research. Journal of clinical epidemiology. 2006 Aug;59(8):849-55.
88. Greenfield S, Blanco DM, Elashoff RM, et al. Patterns of care related to age of breast cancer patients. JAMA: The Journal of the American Medical Association. 1987;257:2766-70.
89. Paleri V, Wight RG, Silver CE, Haigentz Jr M, Takes RP, Bradley PJ, et al. Comorbidity in head and neck cancer: A critical appraisal and recommendations for practice. Oral Oncology. 2010;46(10):712-9.
90. Extermann M. Interaction between comorbidity and cancer. Cancer Control. 2007;14(1):13-22.
91. Nardi R, Scanelli G, Corrao S, Iori I, Mathieu G, Cataldi Amatrian R. Co-morbidity does not reflect complexity in internal medicine patients. European Journal of Internal Medicine. 2007;18(5):359-68.
92. Lin LL, Hahn SM. Combined modality therapy in the elderly population. Current Treatment Options in Oncology. 2009 Aug;10(3-4):195-204.
93. Ogle KS, GM Swanson, N Woods, Azzouz F. Cancer and comorbidity: redefining chronic diseases. Cancer. 2000;88(3):653-63.
94. Octogenarians face poor outcomes from cancer surgery. AORN Journal. 2008;87(3):516-.
95. Amar A, Chedid HM, Franzi SA, Rapoport A. Diagnostic and therapeutic delay in patients with larynx cancer at a reference public hospital. Rev Bras Otorrinolaringol (Engl Ed). 2010 Dec;76(6):700-3.
96. Borggreven PA, Kuik DJ, Langendijk JA, Doornaert P, de Bree R, Leemans CR. Severe comorbidity negatively influences prognosis in patients with oral and oropharyngeal cancer after surgical treatment with microvascular reconstruction. Oral Oncology. 2005 Apr;41(4):358-64.
97. Ries LAG, M Krapcho, DG Stinchcomb, et al. SEER Cancer statistics review 1975-20052010: Available from: http://seer.cancer.gov/statfacts/html/all.html.
98. Safford M, Allison J, Kiefe C. Patient Complexity: More Than Comorbidity. The Vector Model of Complexity. Journal of General Internal Medicine. 2007;22(0):382-90.
99. Charlson ME, Pompei P, Ales KA, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases. 1987;40(5):373-83.
100. Sarfati D, S Hill, et al. The effect of comorbidity on the use of adjuvant chemotherapy and survival from colon cancer: a retrospective cohort study. BMC Cancer. 2009;9(116).
101. Yancik R, Ershler W, Satariano W, Hazzard W, Cohen HJ, Ferrucci L. Report of the national institute on aging task force on comorbidity. J Gerontol A Biol Sci Med Sci. 2007;62(275-280).
102. Sarfati D. Review of methods used to measure comorbidity in cancer populations: No gold standard exists. Journal of clinical epidemiology. 2012;65(9):924-33.
103. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity Measures for Use with Administrative Data. Medical Care. 1998;36(1):8-27.
104. Schaink A, K Kuluski, et al. A scoping review and thematic classification of patient complexity: offering a unifying framework. Journal of Comorbidity. 2012;2:1-9.
105. Sarfati D. Developing new comorbidity indices for cancer populations using administrative data. Dunedin: University of Otago; 2013.
106. Deaton A. Policy Implications Of The Gradient Of Health And Wealth. Health Affairs. 2002 March 1, 2002;21(2):13-30.
107. Liberatos P, Link BG, Kelsey JL. The measurement of social class in epidemiology. Epidemiol Rev. 1988;10:87-121.

108. Groome PA, Schulze KM, Keller S, Mackillop WJ, O'Sullivan B, Irish JC, et al. Explaining Socioeconomic Status Effects in Laryngeal Cancer. Clinical Oncology. 2006;18(4):283-92.
109. Putnam G. 2010 Head and Neck Cancer Annual Evidence Update: Deprivation and Oral cancer2010: Available from: arms.evidence.nhs.uk/resources/hub/35880/attachment.
110. Conway DI, Brewster DH, McKinney PA, Stark J, McMahon AD, Macpherson LMD. Widening socio-economic inequalities in oral cancer incidence in Scotland, 1976-2002. Br J Cancer. 2007;96(5):818-20.
111. Munro AJ. Keynote comment: Deprivation and survival in patients with cancer: we know so much, but do so little. Lancet Oncology. 2005;6:912-13.
112. Gourin CG, Kaboli KC, Blume EJ, Nance MA, Koche WM. Characteristics of participants in a free oral head and neck cancer screening program. The Laryngoscope. 2009;119(4):679-82.
113. Bambra C, M Gibson, A Snowden, K Wright, M Whitehead, M Petticrew. Tackling the wider social determinants of health and health inequalities: evidence from systematic reviews. J Epidemiol Community Health. 2010;64:284-91.
114. Linden G. The influence of social class in the survival of cancer patients. American Journal of Public Health. 1969;59:267-74.
115. Lipworth L, Bennett B, P Parker. Prognosis of non-private cancer patients. J Natl Cancer Inst. 1972;48:11-6.
116. Lipworth L, T Abelin, RR Connelly. Socioeconomic factors in the prognosis of cancer patients. J Chron Dis. 1970;23(2):105-15.
117. Howard J, Lund P, Bell G. Hospital variations in metastatic breast cancer. Med Care. 1980;18:442-55.
118. Krieger N. A glossary for social epidemiology. Journal of Epidemiology and Community Health. 2001 October 1, 2001;55(10):693-700.
119. Department of Health and Social Security. Working Group on Inequalities in Health (The Black Report). Inequalities in health: report of a research working group. London: DHSS; 1980.
120. Department of Health. Towards a healthier Scotland: a white paper on health. In: Health Do, editor. Edinburgh: The Stationery Office; 1999.
121. Shack LG, Rachet B, Brewster DH, Coleman MP. Socioeconomic inequalities in cancer survival in Scotland 1986-2000. Br J Cancer. 2007;97(7):999-1004.
122. Woolley E, Magennis P, Shokar P, Lowe D, Edwards D, Rogers SN The correlation between indices of deprivation and health-related quality of life in patients with oral and oropharyngeal squamous cell carcinoma. British Journal of Oral and Maxillofacial Surgery. 2006;44(3):177-86.
123. Conway DI, McMahon AD, Smith K, Black R, Robertson G, Devine J, et al. Components of socioeconomic risk associated with head and neck cancer: A population-based case–control study in Scotland. British Journal of Oral and Maxillofacial Surgery. 2010;48(1):11-7.
124. Carstairs V, Morris R. Deprivation and health in Scotland. Aberdeen: Aberdeen University Press; 1991.
125. ISD Scotland. Scottish Index of multiple deprivation. Edinburgh: NHS Scotland; 2014 [cited 2011 13 November]; Available from: http://www.isdscotland.org/Products-and-Services/GPD-Support/Deprivation/SIMD/.
126. Cella DF, Orav EJ, Kornblith AB, Holland JC, Silberfarb PM, Lee KW, et al. Socioeconomic status and cancer survival. Journal of Clinical Oncology. 1991 August 1, 1991;9(8):1500-9.
127. Carstairs V, Morris R. Deprivation and health. BMJ. 1989;299(6713):1462.
128. Broder S. Programs and challenges in the National Cancer Program. In: Brugge J, T Curran, E Harlow, F McCormick, editors. Origins of human cancer: A comprehensive review. New York: Cold Spring Harbor Laboratory Press; 1991. p. 21-33.
129. Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. Annals of Oncology. 2006 January 2006;17(1):5-19.

130. Faggiano F, Partanen T, Kogevinas M, Boffetta P. Socioeconomic differences in cancer incidence and mortality. In: Kogevinas M, Pearce N, Susser M, Boffetta P, editors. Social inequalities and cancer. Lyon: IARC; 1997. p. 65-176.
131. World Health Organisation Commission on the Social Determinants of Health. Closing the gap in a generation:health equity through action on the social determinants of health. Geneva: World Health Organisation; 2008.
132. NHS Tayside. Tayside inequalities strategy: Improving health inequalities. Dundee: NHS Tayside; 2003 [cited 2010 20 October]; Available from: http://www.nhstayside.scot.nhs.uk/about_nhstay/publications/health_ineq/Tayside%20Inequalities%20Strategy%20.pdf.
133. Cancer Research UK. Goal8: Low income communities. 2010 [cited 2010 8 December]; Available from: http://www.aboutus.cancerresearchuk.org/who-we-are/our-goals/goal-8-low-income-communities.
134. Mackenbach JP, Kunst A. Measuring the magnitude of socio-economic inequalities in health: and overview of available measures illustrated with two examples from Europe. Social Science Medicine. 1997;44(6):757-71.
135. Louwman WJ, Aarts MJ, Houterman S, van Lenthe FJ, Coebergh JWW, Janssen-Heijnen MLG. A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. Br J Cancer. 2010;103(11):1742-8.
136. Tudor-Hart J. The inverse care law. The Lancet. 1971;297(7696):405-12.
137. Auvinen A, Karjalainen S. Social inequalities and cancer. In: Kogevinas M PN, Susser M, Boffetta P, editor. Lyon: IARC Scientific Publications; 1997. p. 177-206.
138. Hall SF, Rochon PA, Streiner DL, Paszat LF, Groome PA, Rohland SL. Measuring comorbidity in patients with head and neck cancer. Laryngoscope. 2002;112(11):1988-96.
139. Piccirillo JF. Importance of comorbidity in head and neck cancer. Laryngoscope. 2000;110(4):593-602.
140. De Cássia Braga Ribeiro K, Kowalski LP, Do Rosário Dias De Oliveira Latorre M. Impact of comorbidity, symptoms, and patients' characteristics on the prognosis of oral carcinomas. Archives of Otolaryngology - Head and Neck Surgery. 2000;126(9):1079-85.
141. Macleod U, Ross S, Gillis C, McConnachie A, Twelves C, Watt GCM. Socio-economic deprivation and stage of disease at presentation in women with breast cancer. Annals of Oncology. 2000;11:105-07.
142. Richards MA. Foreword. Br J Cancer. 2008;99(S1):S1-S.
143. Piccirillo JF. Impact of comorbidity and symptoms on the prognosis of patients with oral carcinoma. Arch Otolaryngol Head Neck Surg. 2000;126(9):1086-8.
144. Frederiksen BL, Osler M, Harling H, Ladelund S, JÃ¸rgensen T. Do patient characteristics, disease, or treatment explain social inequality in survival from colorectal cancer? Social Science & Medicine. 2009;69(7):1107-15.
145. Munro AJ, Bentley AHM. Deprivation, comorbidity and survival in a cohort of patients with colorectal cancer. Eur J Cancer Care. 2004;13:254-62.
146. Yancik R, Ganz PA, Varricchio CG, Conley B. Perspectives on comorbidity and cancer in older patients: Approaches to expand the knowledge base. Journal of Clinical Oncology. 2001;19(4):1147-51.
147. Piccirillo J. The impact of co-morbidity in head and neck cancer. J Registry Manage. 2001;28:172-76.
148. Piccirillo JF, Costas I. The impact of comorbidity on outcomes. ORL J Otorhinolaryngol Relat Spec. 2004 Jul-Aug;66(4):180-5.
149. Piccirillo JF, Vlahiotis A. Comorbidity in patients with cancer of the head and neck: prevalence and impact on treatment and prognosis. Curr Oncol Rep. 2006 Mar;8(2):123-9.
150. Yung KC, Piccirillo JF. The incidence and impact of comorbidity diagnosed after the onset of head and neck cancer. Archives of Otolaryngology - Head and Neck Surgery. 2008;134(10):1045-9.

151. National Cancer Intelligence Network. Workshop on comorbidity data collection. National Cancer Intelligence Network; 2009 [cited 2011 21 November]; Available from: http://www.ncin.org.uk/collecting_and_using_data/data_collection/comorbidity#workshop.
152. Riley D. Why is comorbidity important for cancer patients? : National Cancer Intelligence Network; 2011 [cited 2011 3 November]; Available from: http://ncin.org/view.aspx?rid=356.
153. Satariano WA. Comorbidities and cancer. In: Hunter CP, Johnson KA, Muss HB, editors. Cancer in the elderly. New York: Marcel Dekker; 2000. p. 477-99.
154. Adami HO, Hunter D, Trichopoulos D. Textbook of Cancer Epidemiology2009.
155. Sanabria A, Carvalho AL, Vartanian JG, Magrin J, Ikeda MK, Kowalski LP. Comorbidity is a prognostic factor in elderly patients with head and neck cancer. Annals of Surgical Oncology. 2007;14(4):1449-57.
156. Alho OP, Hannula K, Luokkala A, Teppo H, Koivunen P, Kantola S. Differential prognostic impact of comorbidity in head and neck cancer. Head and Neck. 2007;29(10):913-8.
157. Hall SF, Groome PA, Irish J, O'Sullivan B. Towards further understanding of prognostic factors for head and neck cancer patients: the example of hypopharyngeal cancer. Laryngoscope. [Research Support, Non-U.S. Gov't]. 2009 Apr;119(4):696-702.
158. Boeje CR, Dalton SO, Primdahl H, Kristensen CA, Andersen E, Johansen J, et al. Evaluation of comorbidity in 9388 head and neck cancer patients: A national cohort study from the DAHANCA database. Radiotherapy and Oncology. 2014;110(1):91-7.
159. Reid BC, Alberg AJ, Klassen AG, Samet JM, Rozier RG, Garcia I, et al. Comorbidity and survival of elderly head and neck carcinoma patients. Cancer. 2001 Oct;92(8):2109-16.
160. Homma A, Sakashita T, Oridate N, Suzuki F, Suzuki S, Hatakeyama H, et al. Importance of comorbidity in hypopharyngeal cancer. Head & Neck. 2010 Feb;32(2):148-53.
161. Chen AY, Matson LK, Roberts D, Goepfert H. The significance of comorbidity in advanced laryngeal cancer. Head and Neck. 2001;23(7):566-72.
162. Ramakrishnan Y, Paleri V, Shah R, Steen IN, Wight RG, Kelly CG. Comorbidity in nasopharyngeal carcinoma: A preliminary communication on the prevalence, descriptive distribution and impact on outcome. Clinical Otolaryngology. 2007;32(6):484-8.
163. Singh B, Bhaya M, Stern J, Roland JT, Zimbler M, Rosenfeld RM, et al. Validation of the Charlson comorbidity index in patients with head and neck cancer: a multi-institutional study. Laryngoscope. 1997 Nov;107(11 Pt 1):1469-75.
164. Sarini J, Fournier C, Lefebvre JL, Bonafos G, Van JT, Coche-Dequeant B. Head and neck squamous cell carcinoma in elderly patients - A long-term retrospective review of 273 cases. Archives of Otolaryngology-Head & Neck Surgery. 2001 Sep;127(9):1089-92.
165. Boeje CR, Dalton SO, Kristensen CA, Andersen E, Johansen J, Andersen LJ, et al. Comorbidity among 13,651 Head and Neck Cancer patients from the dahanca-database. Radiotherapy and Oncology. 2011;98:S5-S6.
166. Merletti F, Galassi C, Spadea T. The socioeconomic determinants of cancer. Environmental Health. 2011;10(Suppl 1):S7.
167. O'Hanlon S, Forster DP, Lowry RJ. Oral cancer in the North East of England: Incidence, mortality trends and the link with material deprivation. Community Dentistry and Oral Epidemiology. 1997;25:371-76.
168. Greenwood M, Thomson PJ, Lowry RJ, Steen IN. Oral cancer: material deprivation, unemployment and risk factor behaviour—an initial study. International Journal of Oral and Maxillofacial Surgery. 2003;32(1):74-7.
169. Kleinschmidt I, Hills M, Elliott P. Smoking behaviour can be predicted by neighbourhood deprivation measures. Jounal of Epidemiology and Community Health. 1995;49(Suppl 2):S72-S7.
170. ISD Scotland. Cancer incidence in Scotland (2010). Edinburgh: Information Services Division; 2011 [cited 2011 23 December]; Available from: http://www.isdscotland.org/Health-Topics/Cancer/Publications/2011-08-30/2011-08-30-Cancer-Incidence-Summary.pdf?30282229186.

171. Bellizi KM, Mustian KM, Bowen DJ, Resnick B, Miller S. Aging in the context of cancer prevention and control: perspectives from behavioural medicine. Cancer. 2008;113(12 Suppl):3479-83.
172. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet. 2008;371:1695-709.
173. Hoffman HT, LH Karnell, GF Funk, RA Robinson, HR Menck. The National Cancer database report on cancer of the head and neck. Arch Otolaryngol Head Neck Surg. 2003;124:951-62.
174. Yancik R, RJ Havlik, MN Wesley, L Ries, et al. Cancer and comorbidities in older patients: a descriptive profile. Ann Epidemiol. 1998;6:399-412.
175. Cancer Research UK. Oral cancer - UK incidence statistics. Cancer Research UK; 2012 [cited 2012 12 May]; Available from: http://info.cancerresearchuk.org/cancerstats/types/oral/incidence/uk-oral-cancer-incidence-statistics.
176. Richards MA. Key challenges for cancer. Transforming inpatient care; July 2010; Leeds2010.
177. Marmot Review. Fair Society, Healthy Lives: Strategic Review of Health Inequalities in England Post 2010. . London: Marmot Review; 2010. p. 242.
178. Gospodarowicz M, O'Sullivan B. Prognostic Factors in Cancer. Seminars in Surgical Oncology. 2003;21:13-8.
179. Anantharaman D, Marron M, Lagiou P, Samoli E, Ahrens W, Pohlabeln H, et al. Population attributable risk of tobacco and alcohol for upper aerodigestive tract cancer. Oral Oncology. 2011;47(8):725-31.
180. Dikshit RP, Boffetta P, Bouchardy C, Merletti F, Crosignani P, Cuchi T, et al. Lifestyle habits as prognostic factors in survival of laryngeal and hypopharyngeal cancer: A multicentric European study. Int J Cancer. 2005;117:992-5.
181. Conway DI, McKinney PA, McMahon AD, Ahrens W, Schmeisser N, Benhamou S, et al. Socioeconomic factors associated with risk of upper aerodigestive tract cancer in Europe. European Journal of Cancer. 2010;46(3):588-98.
182. Schmeisser N, Conway DI, McKinney PA, McMahon AD, Pohlabeln H, Marron M, et al. Life course social mobility and risk of upper aerodigestive tract cancer in men. European Journal of Epidemiology. 2010 Mar;25(3):173-82.
183. Conway DI, M Petticrew, H Marlborough, et al. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. Int J Cancer. 2008;122:2811-9.
184. Freeman HP. Cancer in the socioeconomically disadvantaged. CA Cancer J Clin. 1989;64(1 SUPPL):324-34.
185. Hashibe M, BJ Jacob, G Thomas. Socioeconomic status, lifestyle factors and oral premalignant lesions. Oral Oncol. 2003;39:664-71.
186. Schrijvers CTM, Coebergh JWW, Mackenbach JP. Socioeconomic status and comorbidity among newly diagnosed cancer patients. Cancer. 1997;80(8):1482-8.
187. Montero EH, Trufero JM, Romeo JA, Terré FC. Comorbidity and prognosis in advanced hypopharyngeal-laryngeal cancer under combined therapy. Tumori. 2008;94(1):24-9.
188. van de Schans SAM, Janssen-Heijnen MLG, Biesma B, Smeenk F, van de Poll-Franse LV, Seynaeve C, et al. COPD in cancer patients: Higher prevalence in the elderly, a different treatment strategy in case of primary tumours above the diaphragm, and a worse overall survival in the elderly patient. European Journal of Cancer. 2007 Oct;43(15):2194-202.
189. Kazi R, Nutting CM, Rhys-Evans P, Harrington KJ. Significance and prognostic impact of co-morbidity in head and neck cancer. Journal of Cancer and Research Therapeutics [serial on the Internet]. 2009; 5(3): Available from: http://www.cancerjournal.net/article.asp?issn=0973-1482;year=2009;volume=5;issue=3;spage=145;epage=147;aulast=Kazi.
190. Hurria A. Embracing the Complexity of Comorbidity. Journal of Clinical Oncology. 2011 November 10, 2011;29(32):4217-8.

191. Feinstein AR, Schimpff CR, Andrews JF, Wells CK. Cancer of the larynx: a new staging system and a re-appraisal of prognosis and treatment. J Chronic Dis. 1977;30:277-305.
192. Piccirillo JF, Wells CK, Sasaki CT, Feinstein AR. New clinical severity staging system for cancer of the larynx. Five-year survival rates. Annals of Otology, Rhinology & Laryngology. [Research Support, Non-U.S. Gov't]. 1994 Feb;103(2):83-92.
193. Pugliano FA, Piccirillo JF, Zequeira MR, Emami B, Perez CA, Simpson JR, et al. Clinical-Severity Staging System for Oropharyngeal Cancer: Five-Year Survival Rates. Arch Otolaryngol Head Neck Surg. 1997 October 1, 1997;123(10):1118-24.
194. Boing AF, Antunes JLF. Socioeconomic conditions and head and neck cancer: a systematic literature review. Cien Saude Colet. 2011;16(2):615-22.
195. Hemingway P, Brereton N. What is a systematic review? 2009; Available from: http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/syst-review.pdf.
196. Crombie IK. The pocket guide to critical appraisal. London: BMJ Publishing; 1996.
197. Critical Appraisal Skills Programme (CASP). 10 questions to help you make sense of reviews. Oxford: Public Health Resource Unit, Institute of Health Science; 2006 [cited 2010 3 December]; Available from: http://www.sph.nhs.uk/sph-files/casp-appraisal-tools/S.Reviews%20Appraisal%20Tool.pdf.
198. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of Observational Studies in Epidemiology. JAMA: The Journal of the American Medical Association. 2000 April 19, 2000;283(15):2008-12.
199. Dickersin K. The existence of publication bias and risk factors for its occurrence. Journal of the American Medical Association. 1990;263:1385 - 9.
200. Kopec JL, Esdaile JM. Bias in case control studies. A review. Jounal of Epidemiology and Community Health. 1990;44:179-86.
201. Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, Meu vd, et al. Empirical evidence of designrelated bias in studies of diagnostic tests. JAMA: The Journal of the American Medical Association. 1999;282:106-16.
202. Altman DG. Systematic reviews of evaluations of prognostic variables. BMJ. 2001;323(7306):224-8.
203. Laupacis A, Wells G, Richardson WS, Tugwell P, Group tE-BMW, Guyatt GH, et al. Users' Guides to the Medical Literature. JAMA: The Journal of the American Medical Association. 1994 July 20, 1994;272(3):234-7.
204. Dahm P, Gilbert SM, Zlotecki RA, Guyatt GH. How to Use an Article About Prognosis. The Journal of Urology. 2010;183(4):1303-8.
205. Morris MJ, Fewell AE, Oleszewski RT. Evidence-Based Medicine: Specific Skills Necessary for Developing Expertise in Critical Appraisal. Southern Medical Journal. 2012;105(3):114-9.
206. Evans S, Metcalfe C, Ibrahim F, Persad R, Ben-Shlomo Y. Investigating Black-White differences in prostate cancer prognosis: A systematic review and meta-analysis. Int J Cancer. 2008;123:430-5.
207. Wilczynski N, Haynes RB, Team tH. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. BMC Medicine. 2004;2(1):23.
208. Wilczynski NL, Haynes RB. Optimal search strategies for detecting clinically sound prognostic studies in EMBASE: An analytic survey. Journal of the American Medical Informatics Association. 2005;12(4):481-5.
209. Boyd C, Zhang-Salomons JY, Groome PA, Mackillop WJ. Associations between community income and cancer survival in Ontario, Canada, and the United States. J Clin Oncol. 1999;17:2244-55.
210. Chang T, Chang C, Hsu T, Lin Y, Lai N, et al. The combined effect of individual and neighbourhood socioeconomic status on nasopharyngeal cancer survival. PLoS ONE. 2013;8(9):e73889.
211. Lee C-C, Chien S-H, Hung S-K, Yang W-Z, Su Y-C. Effect of individual and neighborhood socioeconomic status on oral cancer survival. Oral Oncology. 2012;48(3):253-61.

212. McDonald J, Johnson-Obaseki S, Hwang E, Connell C, Corsten M. The relationship between survival and socio-economic status for head and neck cancer in Canada. Journal of Otolaryngology - Head & Neck Surgery. 2014;43(1):2.
213. Peters TTA, Langendijk JA, Plaat BEC, Wedman J, Roodenburg JLN, van Dijk BAC, et al. Co-morbidity and treatment outcomes of elderly pharyngeal cancer patients: A matched control study. Oral Oncology. 2011;47(12):1159-64.
214. Ramroth H, Schoeps A, Rudolph E, Dyckhoff G, Plinkert P, Lippert B, et al. Factors predicting survival after diagnosis of laryngeal cancer. Oral Oncology. 2011;47(12):1154-8.
215. Sadat F, Wienke A, Dunst J, Kuhnt T. Survival of patients with head and neck cancer: impact of physical status and comorbidities. Strahlenther Onkol. 2012 2012/01/01;188(1):62-70.
216. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(6):e1000097.
217. University of Montreal. Critical Appraisal Worksheet. Montreal: University of Montreal; 2004 [cited 2012 16 February]; Available from: http://ktclearinghouse.ca/cebm/teaching/worksheets/prognosis.
218. Sanderson S, Tatt ID, Higgins JPT. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. International Journal of Epidemiology. 2007;36:666–76.
219. Health Evidence Bulletin Wales. Questions to assist with the critical appraisal of an observational study eg cohort, case-control, cross-sectional. Health Evidence Bulletin; 2004; Available from: http://www.cardiff.ac.uk/insrv/libraries/sure/sysnet/pdf/CA%20questions-observational.pdf.
220. Cardarelli R, Oberdorfer JR. Evidence-Based Medicine, Part 5. An Introduction to Critical Appraisal of Articles on Prognosis. JAOA: Journal of the American Osteopathic Association. 2007 August 1, 2007;107(8):315-9.
221. Marx BE, Marx M. Prognosis of idiopathic membranous nephropathy: A methodologic meta-analysis. Kidney Int. 1997;51(3):873-9.
222. Thomas BH, Ciliska D, Dobbins M, Micucci S. A Process for Systematically Reviewing the Literature: Providing the Research Evidence for Public Health Nursing Interventions. Worldviews on Evidence-Based Nursing. 2004;1(3):176-84.
223. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2006;144:427-37.
224. Al-Othman MOF, Morris CG, Logan HL, Hinerman RW, Amdur RJ, Mendenhall WM. Impact of race on outcome after definitive radiotherapy for squamous cell carcinoma of the head and neck. Cancer. 2003 Dec;98(11):2467-72.
225. Franco EL, Dib LL, Pinto DS, Lombardo V, Contesini H. Race and gender influences on the survival of patients with mouth cancer. Journal of clinical epidemiology. 1993;46(1):37-46.
226. Gourin CG, McAfee WJ, Neyman KM, Howington JW, Podolsky RH, Terris DJ. Effect of comorbidity on quality of life and treatment selection in patients with squamous cell carcinoma of the head and neck. Laryngoscope. 2005;115(8):1371-5.
227. Moore SP, Green AC, Garvey G, Coory MD, Valery PC. A study of head and neck cancer treatment and survival among indigenous and non-indigenous people in Queensland, Australia, 1998 to 2004. BMC Cancer. 2011 25 Oct;11(460).
228. Moore RJ, Doherty DA, Do K, Chamberlain RM, Khuri FR. Racial disparity in survival of patients with squamous cell carcinoma of the oral cavity and pharynx. Ethnicity & Health. 2001;6(3/4):165-77.
229. Murdock JM, Gluckman JL. African-American and white head and neck carcinoma patients in a university medical center setting. Are treatments provided and are outcomes similar or disparate? Cancer. 2001 Jan 1;91(1 Suppl):279-83.
230. Ragin CC, Langevin SM, Marzouk M, Grandis J, Taioli E. Determinants of head and neck cancer survival by race. Head and Neck. 2011 August;33(8):1092-8.

231. Schrank TP, Han Y, Weiss H, Resto VA. Case-matching analysis of head and neck squamous cell carcinoma in racial and ethnic minorities in the United States--possible role for human papillomavirus in survival disparities. Head & Neck. 2011 Jan;33(1):45-53.
232. Shiboski CH, Schmidt BL, Jordan RCK. Racial disparity in stage at diagnosis and survival among adults with oral cancer in the US. Community Dentistry and Oral Epidemiology. 2007 Jun;35(3):233-40.
233. Tomar SL, Loree M, Logan H. Racial differences in oral and pharyngeal cancer treatment and survival in Florida. Cancer Causes & Control. 2004 Aug;15(6):601-9.
234. Dequanter D, Shahla M, Paulus P, Boutremans E, Lothaire P. Should older head and neck patients be treated differently? European Annals of Otorhinolaryngology, Head and Neck Diseases. 2011;128(4):165-8.
235. Sethi RA, Stamell EF, Price L, DeLacure M, Sanfilippo N. Head and neck radiotherapy compliance in an underserved patient population. Laryngoscope. 2010 Jul;120(7):1336-41.
236. Bleyer A. Cancer of the Oral Cavity and Pharynx in Young Females: Increasing Incidence, Role of Human Papilloma Virus, and Lack of Survival Improvement. Seminars in Oncology. 2009 October;36(5):451-9.
237. Pintos J, Franco EL, Black MJ, Bergeron J, Arella M. Human papillomavirus and prognoses of patients with cancers of the upper aerodigestive tract. Cancer. 1999;85:1903-9.
238. Settle K, Posner MR, Schumaker LM, Tan M, Suntharalingam M, Goloubeva O, et al. Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients. Cancer Prev Res (Phila Pa). 2009 Sep;2(9):776-81.
239. Bosetti C, Franceschi S, Negri E, Talamini R, Tomei F, La Vecchia C. Changing socioeconomic correlates for cancers of the upper digestive tract. Annals of Oncology. 2001 Mar;12(3):327-30.
240. Freng A, Daae LNW, Engeland A, Norum KR, Sander J, Solvoll K, et al. Malignant epithelial tumours in the upper aerodigestive tract: a dietary and socio-medical case-control and suvival study. European Journal of Clinical Nutrition. 1998;52:271-8.
241. Groome PA, Schulze KM, Keller S, Mackillop WJ. Demographic Differences between Cancer Survivors and those who Die Quickly of their Disease. Clinical Oncology. 2008;20(8):647-56.
242. Johnson S, McDonald JT, Corsten M, Rourke R. Socio-economic status and head and neck cancer incidence in Canada: A case-control study. Oral Oncology. 2010 March;46(3):200-3.
243. Nichols AC, Bhattacharyya N. Racial differences in stage and survival in head and neck squamous cell carcinoma. Laryngoscope. 2007 May;117(5):770-5.
244. Menvielle G, Kunst AE, Stirbu I, Borrell C, Bopp M, Regidor E, et al. Socioeconomic inequalities in alcohol related cancer mortality among men: To what extent do they differ between Western European populations? International Journal of Cancer. 2007 Aug;121(3):649-55.
245. Moles DR, Fedele S, Speight PM, Porter SR, Silva ID. Oral and pharyngeal cancer in South Asians and non-South Asians in relation to socioeconomic deprivation in South East England. British Journal of Cancer. 2008 Feb;98(3):633-5.
246. Menvielle G, Luce D, Goldberg P, Leclerc A. Smoking, alcohol drinking, occupational exposures and social inequalities in hypopharyngeal and laryngeal cancer. International Journal of Epidemiology. 2004 Aug;33(4):799-806.
247. Nobles J, Wold C, Fazekas-May M, Gilbert J, Friedlander PL. Prevalence and epidemiology of hepatitis C virus in patients with squamous cell carcinoma of the head and neck. Laryngoscope. 2004 Dec;114(12):2119-22.
248. Patel RS, McCluskey SA, Goldstein DP, Minkovich L, Irish JC, Brown DH, et al. Clinicopathologic and therapeutic risk factors for perioperative complications and prolonged hospital stay in free flap reconstruction of the head and neck. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck. 2010 Oct;32(10):1345-53.
249. Vartanian JG, Carvalho AL, Toyota J, Kowalski ISG, Kowalski LP. Socioeconomic effects of and risk factors for disability in long-term survivors of head and neck cancer. Arch Otolaryngol Head Neck Surg. [Comparative Study]. 2006 Jan;132(1):32-5.

250. Wutzl A, Ploder O, Kermer C, Millesi W, Ewers R, Klug C. Mortality and causes of death after multimodality treatment for advanced oral and oropharyngeal cancer. Journal of Oral & Maxillofacial Surgery. 2007 Feb;65(2):255-60.
251. Goeman JJ, Le Cessie S, de Jong RJB, van de Geer SA. Predicting survival using disease history: a model combining relative survival and frailty. Statistica Neerlandica. 2004 Feb;58(1):21-34.
252. Antunes JL, Biazevic MG, de Araujo ME, Tomita NE, Chinellato LE, Narvai PC. Trends and spatial distribution of oral cancer mortality in Sao Paulo, Brazil, 1980-1998. Oral Oncology. 2001 Jun;37(4):345-50.
253. de Cassia Braga Ribeiro K, Kowalski LP, Latorre MdRDdO. Perioperative complications, comorbidities, and survival in oral or oropharyngeal cancer. Arch Otolaryngol Head Neck Surg. 2003 Feb;129(2):219-28.
254. Ahmad H, Jabar NA, Rahman NA, Rahman RA, Sha PP, Ramli R. Oral cavity squamous cell carcinomas in young patients in a selected Malaysian centre. Asia-Pacific Journal of Clinical Oncology. 2009 Mar;5(1):39-45.
255. Zigon G, Berrino F, Gatta G, Sanchez MJ, van Dijk B, Van Eycken E, et al. Prognoses for head and neck cancers in Europe diagnosed in 1995-1999: a population-based study. Annals of Oncology. 2011 Jan;22(1):165-74.
256. Rogers SN, Brown JS, Woolgar JA, Lowe D, Magennis P, Shaw RJ, et al. Survival following primary surgery for oral cancer. Oral Oncology. 2009 Mar;45(3):201-11.
257. Grandis JR, Snyderman CH, Johnson JT, Yu VL, D'Amico F. Postoperative wound infection. Cancer. 1992;70:2166-70.
258. Ferrier MB, Spuesens EB, Le Cessie S, Baatenburg De Jong RJ. Comorbidity as a major risk factor for mortality and complications in head and neck surgery. Archives of Otolaryngology - Head and Neck Surgery. 2005;131(1):27-32.
259. Zeber JE, Copeland LA, Hosek BJ, Karnad AB, Lawrence VA, Sanchez-Reilly SE. Cancer rates, medical comorbidities, and treatment modalities in the oldest patients. Critical Reviews in Oncology/Hematology. 2008;67(3):237-42.
260. Coatesworth AP, Tsikoudas A, MacLennan K. The cause of death in patients with head and neck squamous cell carcinoma. Journal of Laryngology & Otology. 2002;116:269-71.
261. Jones AS, Beaseley N, Houghton D, Husband DJ. The effects of age on survival and other parameters in squamous cell carcinoma of the oral cavity, pharynx and larynx. Clinical Otolaryngology. 1998;23:51-6.
262. Kruse AL, Bredell M, Luebbers HT, Gratz KW. Head and neck cancer in the elderly: a retrospective study over 10 years (1999 - 2008). Head & Neck Oncology. 2010;2:25.
263. Su C-C, Chung J-A, Hsu Y-Y, Huang S-J, Lian I-B. Age at diagnosis and prognosis of oral cancer in relation to the patient's residential area: experience from a medical center in Taiwan. Oral Oncology. 2008 Nov;44(11):1032-8.
264. Lee MK, Nalliah RP, Kim MK, Elangovan S, Allareddy V, Kumar-Gajendrareddy P. Prevalence and impact of complications on outcomes in patients hospitalized for oral and oropharyngeal cancer treatment. Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontology. 2011 Nov;112(5):581-91.
265. de Melo GM, Ribeiro KC, Kowalski LP, Deheinzelin D. Risk factors for postoperative complications in oral cancer and their prognostic implications. Arch Otolaryngol Head Neck Surg. 2001 Jul;127(7):828-33.
266. Avery CM, Crank ST, Neal CP, Hayter JP, Elton C. The use of the pectoralis major flap for advanced and recurrent head and neck malignancy in the medically compromised patient. Oral Oncology. 2010;46(11):829-33.
267. Baatenburg De Jong RJ, Hermans J, Molenaar J, et al. Prediction of survival in patients with head and neck cancer. Head Neck. 2001;23:718-24.

268. El-Deiry MW, Futran ND, McDowell JA, Weymuller EA, Yueh B. Influences and predictors of long-term quality of life in head and neck cancer survivors. Archives of Otolaryngology - Head and Neck Surgery. 2009;135(4):380-4.
269. Kantola S, Parikka M, Jokinen K, Hyrynkangs K, Soini Y, Alho OP, et al. Prognostic factors in tongue cancer - relative importance of demographic, clinical and histopathological factors. British Journal of Cancer. 2000 Sep;83(5):614-9.
270. van der Schroeff MP, van de Schans SAM, Piccirillo JF, Langeveld TPM, Baatenburg de Jong RJ, Janssen-Heijnen MLG. Conditional relative survival in head and neck squamous cell carcinoma: Permanent excess mortality risk for long-term survivors. Head & Neck. 2010 Dec;32(12):1613-8.
271. Antunes JLF, Borrell C, Perez G, Boing AF, Wunsch V. Inequalities in mortality of men by oral and pharyngeal cancer in Barcelona, Spain and Sao Paulo, Brazil, 1995-2003. International Journal for Equity in Health. 2008;7.
272. Cinamon U, Hier MP, Black MJ. Age as a prognostic factor for head and neck squamous cell carcinoma: should older patients be treated differently? J Otolaryngol. 2006 Feb;35(1):8-12.
273. Du XLL, Liu CC. Racial/Ethnic Disparities in Socioeconomic Status, Diagnosis, Treatment and Survival among Medicare-insured Men and Women with Head and Neck Cancer. Journal of Health Care for the Poor and Underserved. 2010 Aug;21(3):913-30.
274. Gorey KM, Holowaty EJ, Laukkanen E, Fehringer G, Richter NL. An international comparison of cancer survival: advantage of Toronto's poor over the near poor of Detroit. Canadian Journal of Public Health. 1998;89(2):102-4.
275. Routh A, Hickman BT. The influence of socio-economic status on prognosis of patients with cancer of the tongue after radiotherapy. Radiat Med. 1991 Jan-Feb;9(1):26-8.
276. Sabin SL, Rosenfeld RM, Sundaram K, Har-el G, Lucente FE. The impact of comorbidity and age on survival with laryngeal cancer. Ear Nose Throat J. 1999 Aug;78(8):578, 81-4.
277. Manton KG, Wrigley JM, Cohen HJ, Woodbury MA. Cancer mortality, aging, and patterns of comorbidity in the United States: 1968 to 1986. Journal of gerontology. 1991;46(4):S225-34.
278. Brown KW, Levy AR, Roseberger Z, Edgar L. Psychological distress and cancer survival: a follow-up 10years after diagnosis. Pychosomatic Medicine. 2003;65:636-43.
279. Jeffreys M, Sarfati D, Stevanovic V, Tobias M, Lewis C, Pearce N, et al. Socioeconomic inequalities in cancer survival in New Zealand: The role of extent of disease at diagnosis. Cancer Epidemiology Biomarkers and Prevention. 2009 March;18(3):915-21.
280. Schrijvers CT, Coebergh JWW, Mackenbach JP. Socioeconomic status and comorbidity among newly diagnosed cancer patients. Cancer. 1997;80:1482-8.
281. Ueda K, Tsukuma H, Ajiki W, Oshima A. Socioeconomic factors and cancer incidence, mortality, and survival in a metropolitan area of Japan: A cross-sectional ecological study. Cancer Science. 2005;96(10):684-8.
282. Sloggett A, Young H, Grundy E. The association of cancer survival with four socioeconomic indicators: a longitudinal study of the older population of England and Wales 1981-2000. BMC Cancer. 2007;7(1):20.
283. Nouraei SAR, Al-Yaghchi C, Sandhu GS, Giussani DA, Doyle P, Clarke PM. Incidence and significance of myocardial injury after surgical treatment of head and neck cancer. Laryngoscope. 2007 Sep;117(9):1581-7.
284. Moore CE, Durden F. Head and neck cancer screening in homeless communities: HEAL (Health Education, Assessment, and Leadership). Journal of the National Medical Association. 2010 September;102(9):811-6.
285. Peters TTA, van der Laan B, Plaat BEC, Wedman J, Langendijk JA, Halmos GB. The impact of comorbidity on treatment-related side effects in older patients with laryngeal cancer. Oral Oncology. 2011 Jan;47(1):56-61.
286. Nagele P, Rao LK, Penta M, Kallogjeri D, Spitznagel EL, Cavallone LF, et al. Postoperative myocardial injury after major head and neck surgery Head and Neck-Journal for the Sciences and Specialties of the Head and Neck. 2011 Aug;33(8):1085-91.

287. Zabrodsky M, Calabrese L, Tosoni A, Ansarin M, Giugliano G, Bruschini R, et al. Major surgery in elderly head and neck cancer patients: immediate and long-term surgical results and complication rates. Surg Oncol. 2004 Dec;13(4):249-55.
288. Pytynia KB, Grant JR, Etzel CJ, Roberts D, Wei Q, Sturgis EM. Matched analysis of survival in patients with squamous cell carcinoma of the head and neck diagnosed before and after 40 years of age. Archives of Otolaryngology - Head & Neck Surgery. 2004;130(7):869-73.
289. Hansen RP, Olesen F, Sorensen HT, Sokolowski I, Sondergaard J. Socioeconomic patient characteristics predict delay in cancer diagnosis: a Danish cohort study. Bmc Health Services Research. 2008;8:49-58.
290. Teppo H, Alho OP. Comorbidity and diagnostic delay in cancer of the larynx, tongue and pharynx. Oral Oncology. 2009;45(8):692-5.
291. Grignon LM, Jameson MJ, Karnell LH, Christensen AJ, Funk GF. General health measures and long-term survival in patients with head and neck cancer. Archives of Otolaryngology - Head and Neck Surgery. 2007;133(5):471-6.
292. Jameson MJ, Karnell LH, Christensen AJ, Funk GF. First-year trends in self-reported general health predict survival in patients with head and neck cancer. Archives of Otolaryngology-Head & Neck Surgery. 2008 Sep;134(9):958-64.
293. Cederblad L, Johansson S, Enblad G, Engstrom M, Blomquist E. Cancer of the parotid gland; long-term follow-up. A single centre experience on recurrence and survival. Acta Oncologica. 2009;48(4):549-55.
294. Hall SF, Groome PA, Rothwell D. The impact of comorbidity on the survival of patients with squamous cell carcinoma of the head and neck. Head and Neck. 2000;22(4):317-22.
295. Major MS, Bumpous JM, Flynn MB, Schill K. Quality of life after treatment for advanced laryngeal and hypopharyngeal cancer. Laryngoscope. 2001;111(8):1379-82.
296. Tong H, Isenring E, Yates P. The prevalence of nutrition impact symptoms and their relationship to quality of life and clinical outcomes in medical oncology patients. Supportive Care in Cancer. 2009 January;17(1):83-90.
297. Francis DO, Yueh B, Weymuller EA, Merati AL. Impact of Surveillance on Survival After Laryngeal Cancer in the Medicare Population. Laryngoscope. 2009 Dec;119(12):2337-44.
298. Argiris A, Brockstein BE, Haraf DJ, Stenson KM, Mittal BB, Kies MS, et al. Competing Causes of Death and Second Primary Tumors in Patients with Locoregionally Advanced Head and Neck Cancer Treated with Chemoradiotherapy. Clinical Cancer Research. 2004;10(6):1956-62.
299. Paleri V, Wight RG. A cross-comparison of retrospective notes extraction and combined notes extraction and patient interview in the completion of a comorbidity index (ACE-27) in a cohort of United Kingdom patients with head and neck cancer. Journal of Laryngology and Otology. 2002;116(11):937-41.
300. Rogers S, Kenyon P, Lowe D, Grant C, Dempsey G. The relation between health-related quality of life, past medical history, and American Society of Anesthesiologists' ASA grade in patients having primary operations for oral and oropharyngeal cancer. British Journal of Oral & Maxillofacial Surgery. 2005 Apr;43(2):134-43.
301. Piccirillo JF, Spitznagel EL, Vermoni N, Costas I, Schnitzler M. Comparison of comorbidity indices for patients with head and neck cancer. Medical Care. 2004;42(5):482-6.
302. Babin E, Sigston E, Hitier M, Dehesdin D, Marie JP, Choussy O. Quality of life in head and neck cancers patients: Predictive factors, functional and psychosocial outcome. European Archives of Oto-Rhino-Laryngology. 2008 Mar;265(3):265-70.
303. Allison P, Locker D, Feine JS. The role of diagnostic delays in the prognosis of oral cancer: a review of the literature. Oral Oncology. 1998 May;34(3):161-70.
304. Rudolph E, Dyckhoff G, Becher H, Dietz A, Ramroth H. Effects of tumour stage, comorbidity and therapy on survival of laryngeal cancer patients: a systematic review and a meta-analysis. European Archives of Oto-Rhino-Laryngology. 2011 2011/02/01;268(2):165-79.

305. Nutting CM, Robinson M, Birchall M. Survival from laryngeal cancer in England and Wales up to 2001 - Commentary. British Journal of Cancer. 2008 23 Sep;99(SUPPL.1):S38-S9.
306. Casasola RJ. Head and neck cancer. J R Coll Physicians Edinb. 2010 Dec;40(4):343-5; quiz 5.
307. Archer J, Hutchison I, Korszun A. Mood and malignancy: Head and neck cancer and depression. Journal of Oral Pathology and Medicine. 2008;37(5):255-70.
308. Rosenberg PS, Socie G, Alter BP, Gluckman E. Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants. Blood. 2005 01 Jan;105(1):67-73.
309. Coleman MP, Babb P, Sloggett A, Quinn M, De Stavola B. Socioeconomic inequalities in cancer survival in England and Wales. Cancer. 2001;91:208-16.
310. Deleyiannis FWB, DB' T, Vaughan SL, Davis S. Alcoholism: Independent predictor of survival in patients with head and neck cancer. Journal of the National Cancer Institute. 1996;88(8):542-9.
311. Arbes Jr SJ. Factors contributing to the poorer survival of black Americans diagnosed with oral cancer (United States). Cancer Causes and Control. 1999;10(6):513-23.
312. Read WL, Tierney RM, Page NC, Costas I, Govindan R, Spitznagel EL, et al. Differential prognostic impact of comorbidity. J Clin Oncol. 2004;22:3099-103.
313. De Boer MF, Van den Borne B, Pruyn JF, Ryckman RM, Volovics L, Knegt PP, et al. Psychosocial and physical correlates of survival and recurrence in patients with head and neck carcinoma: results of a 6-year longitudinal study. Cancer. 1998;83(12):2567-79.
314. Faye-Lund H, Abdelnoor M. Prognostic factors of survival in a cohort of head and neck cancer patients in Oslo. Eur J Cancer B Oral Oncol. 2006;32B:83-90.
315. Chirikos TN, Reiches NA, Moeschberger ML. Economic differentials in cancer survival a multivariate analysis. J Chron Dis. 1984;37:183-93.
316. El-Husseiny G, Kandil A, Jamshed A, et al. Squamous cell carcinoma of the oral tongue: an analysis of prognostic factors. British Journal of Oral & Maxillofacial Surgery. 2000;38:193-9.
317. Australian Institute of Health and Welfare. Cancer survival in Australia 1992-1997. Geographic categories and socioeconomic status. Canberra: AIHW2003.
318. Magnano M, De Stefani A, Usai A, Lerda W, Albera R, Ragona R, et al. Carcinoma of the larynx in the elderly: analysis of potentially significant prognostic variables. Aging (Milano). 1999;5:316-22.
319. Rose BS, Jeong JH, Nath SK, Lu SM, Mell LK. Population-based study of competing mortality in head and neck cancer. Journal of Clinical Oncology. 2011;29(26):3503-9.
320. Steyerberg EW, Neville B, Weeks JC, Earle CC. Referral patterns, treatment choices, and outcomes in locoregional esophageal cancer: a population-based analysis of elderly patients. Journal of Clinical Oncology. 2007;25(17):2389-96.
321. Cheung MC, Franzmann E, Sola JE, Pincus DJ, Koniaris LG. A Comprehensive Analysis of Parotid and Salivary Gland Cancer: Worse Outcomes for Male Gender. Journal of Surgical Research. 2011 Nov;171(1):151-8.
322. Sharma A, Schwartz SM, Mendez E. Hospital volume is associated with survival but not multimodality therapy in Medicare patients with advanced head and neck cancer. Cancer. 2013;119(10):1845-52.
323. Zhu J, Fedewa S, Chen AY. The impact of comorbidity on treatment (chemoradiation and laryngectomy) of advanced, non distant metastatic laryngeal cancer: a review of 16849 cases from the national cancer database (2003-2008). Arch Otolaryngol Head Neck Surg. 2012;138(12):1120-8.
324. Reyes-Gibby CC, Ba Duc N, Phi Yen N, Hoai Nga N, Van Tran T, Guo H, et al. Status of Cancer Pain in Hanoi, Vietnam: A Hospital-Wide Survey in a Tertiary Cancer Treatment Center. Journal of Pain and Symptom Management. 2006 May;31(5):431-9.
325. Petticrew M, Roberts H. Systematic reviews in social sciences: a practical guide. Oxford: Wiley Blackwell; 2006.
326. Tierney J, Stewart L, Ghersi D, Burdett S, Sydes M. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8(1):16.

327. Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Systematic reviews of trials and other studies: Review. Southampton: University of Southampton1998 Contract No.: 19.
328. Therneau TM. A Package for Survival Analysis in S. 2015 [cited 2015 6 March]; version 2.38:[Available from: http://CRAN.R-project.org/package=survival.
329. Hedges LV. Statistical considerations. In: Cooper H, Hedges LV, editors. The handbook of research synthesis. New York: Russell Sage Foundation; 1994.
330. Datema FR, MB Ferrier, MP van der Schroeff, RJ Baatenburg de Jong. Impact of comorbidity on short-term mortality and overall survival of head and neck cancer patients. Head & Neck. 2010;32(6):728-36.
331. Terhaard CH, van der Schroeff MP, van Schie K, Eerenstein SE, Lubsen H, Kaanders JH, et al. The prognostic role of comorbidity in salivary gland carcinoma. Cancer. 2008;113(7):1572-9.
332. Ledeboer QCP, van der Schroeff MP, Pruyn JFA, de Boer MF, de Jong RJB, van der Velden LA. Survival of patients with palliative head and neck cancer. Head and Neck. 2011 Jul;33(7):1021-6.
333. Tanvetyanon T, Padhya T, McCaffrey J, Zhu W, Boulware D, Deconti R, et al. Prognostic factors for survival after salvage reirradiation of head and neck cancer. Journal of Clinical Oncology. 2009;27(12):1983-91.
334. Soares M, Salluh JIF, Toscano L, Dias FL. Outcomes and prognostic factors in patients with head and neck cancer and severe acute illnesses. Intensive Care Med. 2007 Nov;33(11):2009-13.
335. Reid BC, Alberg AJ, Klassen AC, Samet JM, Rozier RG, Garcia I, et al. Comorbidity and survival of elderly head and neck carcinoma patients. Cancer. [Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.]. 2001 Oct 15;92(8):2109-16.
336. Ghobadi A, Athar M, Dowell J. The incidence and impact of comorbidity on survival and selection of initial treatment in elderly patients (pts) with head and neck cancer (HNC). Journal of Clinical Oncology. 2009;1):6065.
337. Liu CT, Chiu TJ, Huang TL, Chien CY, Fang FM. Impact of comorbidity on survival for locally advanced head and neck cancer patients treated by radiotherapy or radiotherapy plus chemotherapy. Chang Gung Medical Journal. 2010 May - June;33(3):283-91.
338. Gimeno-Hernáández J, Iglesias-Moreno M-C, Góómez-Serrano M, Carricondo F, Gil-Loyzaga P, Poch-Broto J. The impact of comorbidity on the survival of patients with laryngeal squamous cell carcinoma. Acta Oto-Laryngologica. 2011;131(8):840-6.
339. Mell LK, Dignam JJ, Salama JK, Cohen EE, Polite BN, Dandekar V, et al. Predictors of competing mortality in advanced head and neck cancer. Journal of Clinical Oncology. 2010 2010 Jan 1;28(1):15-20.
340. Gourin CG, Podolsky RH. Racial disparities in patients with head and neck squamous cell carcinoma. Laryngoscope. 2006 Jul;116(7):1093-106.
341. Allareddy V, Konety BR. Characteristics of patients and predictors of in-hospital mortality after hospitalization for head and neck cancers. Cancer. 2006;106(11):2382-8.
342. Gimeno-Hernandez J, Iglesias-Moreno MC, Gomez-Serrano M, Carricondo F, Gil-Loyzaga P, Poch-Broto J. The impact of comorbidity on the survival of patients with laryngeal squamous cell carcinoma. Acta Oto-Laryngologica. 2011 Aug;131(8):840-6.
343. Pedruzzi PAG, Kowalski LP, Nishimoto IN, Oliveira BV, Tironi F, Ramos GHA. Analysis of prognostic factors in patients with oropharyngeal squamous cell carcinoma treated with radiotherapy alone or in combination with systemic chemotherapy. Arch Otolaryngol Head Neck Surg. 2008 Nov;134(11):1196-204.
344. Datema FR, Ferrier MB, Baatenburg de Jong RJ. Impact of severe malnutrition on short-term mortality and overall survival in head and neck cancer. Oral Oncology. 2011 Sep;47(9):910-4.
345. Leitner C, Rogers SN, Lowe D, Magennis P. Death certification in patients whose primary treatment for oral and oropharyngeal carcinoma was operation: 1992-1997. British Journal of Oral & Maxillofacial Surgery. 2001 Jun;39(3):204-9.

346. Sanabria A, Carvalho AL, Vartanian JG, Magrin J, Ikeda MK. Validation of the Washington University Head and Neck Comorbidity Index in a cohort of older patients. Archives of Otolaryngology - Head & Neck Surgery. 2008;134(6):603-7.
347. Wu C-H, Wu T-Y, Li C-C, Lui M-T, Chang K-W, Kao S-Y. Impact of diabetes mellitus on the prognosis of patients with oral squamous cell carcinoma: a retrospective cohort study. Annals of Surgical Oncology. 2010 Aug;17(8):2175-83.
348. Yang C-C, Chen P-C, Hsu C-W, Chang S-L, Lee C-C. Validity of the Age-Adjusted Charlson Comorbidity Index on Clinical Outcomes for Patients with Nasopharyngeal Cancer Post Radiation Treatment: A 5-Year Nationwide Cohort Study. PLoS ONE. 2015;10(1):e0117323.
349. Zhang S-Y, Lu Z-M, Luo X-N, Chen L-S, Ge P-J, Song X-H, et al. Retrospective Analysis of Prognostic Factors in 205 Patients with Laryngeal Squamous Cell Carcinoma Who Underwent Surgical Treatment. PLoS ONE. 2013;8(4):e60157.
350. Schans van de SAM, Janssen-Heijnen MLG, Biesma B, Smeenk F, van de Poll-Franse LV, Seynaeve C, et al. COPD in cancer patients: Higher prevalence in the elderly, a different treatment strategy in case of primary tumours above the diaphragm, and a worse overall survival in the elderly patient. European Journal of Cancer. 2007;43(15):2194-202.
351. Woodard TD, Oplatek A, Petruzzelli GJ. Life after total laryngectomy - A measure of long-term survival, function, and quality of life. Archives of Otolaryngology-Head & Neck Surgery. 2007 Jun;133(6):526-32.
352. Liu H, Xia Y, Cui N. Impact of diabetes mellitus on treatment outcomes in patients with nasopharyngeal cancer. Med Oncol. 2006;23(3):341-6.
353. Paterson ICM, John G, Adams Jones D. Effect of Deprivation on Survival of Patients with Head and Neck Cancer: a Study of 20,131 Cases. Clinical Oncology. 2002;14(6):455-8.
354. Anandan C, Elton R, Hitchings A, Brewster DH. Nasopharyngeal cancer incidence and survival in Scotland, 1975-2001. Clinical Otolaryngology. 2008 Feb;33(1):12-7.
355. Edwards DM, Jones J. Incidence of and survival from upper aerodigestive tract cancers in the U.K.: the influence of deprivation. European Journal of Cancer. 1999 Jun;35(6):968-72.
356. Boffetta P, Merletti F, Faggiano F, Migliaretti G, Ferro G, Zanetti R, et al. Prognostic factors and survival of laryngeal cancer patients from Turin, Italy. A population-based study. American Journal of Epidemiology. 1997 Jun 15;145(12):1100-5.
357. Warnakulasuriya S, Mak V, Moller H. Oral cancer survival in young people in South East England. Oral Oncology. 2007 Nov;43(10):982-6.
358. Robertson G, Greenlaw N, Bray CA, Morrison DS, Steering Grp Comm Scottish Audit H. Explaining the effects of socio-economic deprivation on survival in a national prospective cohort study of 1909 patients with head and neck cancers. Cancer Epidemiology. 2010 Dec;34(6):682-8.
359. Mackillop WJ, Zhang-Salomons J, Groome PA, Paszat L, Holowaty E. Socioeconomic status and cancer survival in Ontario. J Clin Oncol. 1997;15:1680-89.
360. Chu KP, Habbous S, Huang S, Cheng L, Hope A, Xu W, et al. Impact of Socioeconomic Status (SES) on Head and Neck Cancer (HNC) Survival in an Equal Access Health Care System. International Journal of Radiation Oncology Biology Physics. 2011;81(2):S107-S8.
361. de Graeff A, de Leeuw JR, Ros WJ, Hordijk GJ, Blijham GH, Winnubst JA. Sociodemographic factors and quality of life as prognostic indicators in head and neck cancer. European Journal of Cancer. 2001 Feb;37(3):332-9.
362. Chu K, Shema S, Wu S, Gomez S, Chang E, Le QT. Head and neck cancer specific survival based on socioeconomic status in asian-pacific islanders. Radiotherapy and Oncology. 2010;96:S54.
363. Rachet B, Quinn MJ, Cooper N, Coleman MP. Survival from cancer of the larynx in England and Wales up to 2001. British Journal of Cancer. 2008 Sep 23;99 Suppl 1:S35-7.
364. Chu KP, Shema S, Wu S, Gomez SL, Chang ET, Le Q-T. Head and neck cancer-specific survival based on socioeconomic status in Asians and Pacific Islanders. Cancer. 2011 May 1;117(9):1935-45.

365. Jovanovic-Andersen Z, Lassen CF, Clemmensen IH. Social inequality incidence of and survival from cancers of the mouth, pharynx and larynx in a population based study in Denmark 1994-2003. Eur J Cancer. 2008;44:1950-61.
366. Reitzel LR, Nguyen N, Zafereo ME, Li G, Wei Q, Sturgis EM. Neighborhood deprivation and clinical outcomes among head and neck cancer patients. Health Place. 2012;18(4):861-8.
367. Kwok J, Langevin SM, Argiris A, Grandis JR, Gooding WE, Taioli E. The impact of health insurance status on the survival of patients with head and neck cancer. Cancer. 2010 Jan 15;116(2):476-85.
368. Konski A, Berkey BA, Ang KK, Fu KK. Effect of education level on outcome of patients treated on radiation therapy oncology group protocol 90-03. Cancer. 2003 01 Oct;98(7):1497-503.
369. Puigpinos R, Borrell C, Antunes JLF, Azlor E, Pasarin MI, Serral G, et al. Trends in socioeconomic inequalities in cancer mortality in Barcelona: 1992-2003. BMC Public Health. 2009;9:35.
370. Rosso S, Faggiano F, Zanetti R, Costa G. Social class and cancer survival in Turin, Italy. Journal of Epidemiology & Community Health. 1997 Feb;51(1):30-4.
371. Menvielle G, Leclerc A, Chastang JF, Melchior M, Luce D. Changes in socioeconomic inequalities in cancer mortality rates among French men between 1968 and 1996. American Journal of Public Health. 2007;97(11):2082-7.
372. Wong Y-K, Tsai W-C, Lin J-C, Poon C-K, Chao S-Y, Hsiao Y-L, et al. Socio-demographic factors in the prognosis of oral cancer patients. Oral Oncology. 2006 Oct;42(9):893-906.
373. Alicikus ZA, Akman F, Ataman OU, Dag N, Orcin E, Bakis B, et al. Importance of patient, tumour and treatment related factors on quality of life in head and neck cancer patients after definitive treatment. European Archives of Oto-Rhino-Laryngology. 2009 September;266(9):1461-8.
374. Piccirillo JF, Lacy PD, Basu A, Spitznagel EL. Development of a new head and neck cancer-specific comorbidity index. Archives of Otolaryngology - Head and Neck Surgery. 2002;128(10):1172-9.
375. Warnakulasuriya KA, CK Harris, DM Scarrot, al e. An alarming lack of public awareness towards oral cancer. Br Dental J. 1999;187:319-22.
376. Carter LM, Ogden GR. Oral cancer awareness of undergraduate medical and dental students. BMC Med Educ. 2007;7:44.
377. Institute of Medicine. Unequal treatment confronting racial disparities in health care. Washington DC: National Academies Press; 2003.
378. Faggiano F, Zanetti R, Costa G. Cancer risk and social inequalities in Italy. J Epidemiol Community Health. 1994;48:447-52.
379. Pignon J. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative GrouMeta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet. 2000;355(9208):949 - 55.
380. Guralnik JM. Assessing the impact of comorbidity in the older population. Annals of Epidemiology. 1996;6(5):376-80.
381. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson AB, et al. Impact of Diabetes Mellitus on Outcomes in Patients With Colon Cancer. Journal of Clinical Oncology. 2003 February 1, 2003;21(3):433-40.
382. Kogevinas M, Marmot MG, Fox AJ, Goldblatt PO. Socioeconomic differences in cancer survival. Journal of Epidemiology and Community Health. 1991 September 1, 1991;45(3):216-9.
383. Duffy SA, Khan MJ, Ronis DL, Fowler KE, Gruber SB, Wolf GT, et al. Health Behaviors of Head and Neck Cancer Patients the First Year after Diagnosis. Head & Neck. 2008;30:93-102.
384. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, et al. Distinct Risk Factor Profiles for Human Papillomavirus Type 16 Positive and Human Papillomavirus Type 16 Negative Head and Neck Cancers. Journal of the National Cancer Institute. 2008 March 19, 2008;100(6):407-20.

385. Martinez I. Identification of differentially expressed genes in HPV-positive and HPV-negative oropharyngeal squamous cell carcinomas. Eur J Cancer. 2007;43(2):415 - 32.
386. Hoffman M, Gorogh T, Gottschlich S, Lohrey C, Rittgren W, Ambrosch P, et al. Human papilloma viruses in head and neck cancer: 8 year analysis of 73 patients. Cancer Letters. 2005;219:199-206.
387. Information Services Division. Trends in cancer survival in Scotland, 1983-2007. 2011 [cited 2010 23 November]; Available from: http://www.isdscotlandarchive.scot.nhs.uk/isd/files/Survival_summary_8307.pdf.
388. Pampel FC, Kreuger PM, Denney JT. Socioeconomic disparities in health behaviours. Annual Review of Sociology. 2010;36:349-70.
389. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, et al. Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer. New England Journal of Medicine. 2007;356(19):1944-56.
390. Hansson B. Strong association between infection with human papillomavirus and oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. Acta Otolaryngol. 2005;125(12):1337 - 44.
391. Rosenquist K. Oral status, oral infections and some lifestyle factors as risk factors for oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. Acta Otolaryngol. 2005;125(12):1327 - 36.
392. Habbous S, Harland LTG, La Delfa A, Fadhel E, Xu W, Liu F-F, et al. Comorbidity and prognosis in head and neck cancers: Differences by subsite, stage, and human papillomavirus status. Head & Neck. 2014;36(6):802-10.
393. Joseph AW, Pai SI. Human papillomavirus and the shifting trends in head and neck cancer2011: Available from: http://www.asco.org/ASCOv2/Home/Education%20%26%20Training/Educational%20Book/PDF%20Files/2011/zds00111000212.PDF.
394. Mannarini L, Kratochvili L, Calabrese L, Gomes Silva L, Morbini P, Betkai J, et al. Human Papilloma Virus (HPV) in head and neck region: review of literature. Acta Otolaryngologica Italica. 2009;29:119-26.
395. Massano J, Regateiro FS, Januario G, Ferreira A. Oral squamous cell carcinoma: review of prognostic and predictive factors. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006 Jul;102(1):67-76.
396. O'Rorke MA, Ellison MV, Murray LJ, Moran M, James J, Anderson LA. Human papillomavirus related head and neck cancer survival: A systematic review and meta-analysis. Oral Oncology. 2012;48:1191-201.
397. Ragin CCR, Taioli E. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: Review and meta-analysis. International Journal of Cancer. 2007;121(8):1813-20.
398. Antonovsky A. The salutogenic model as a theory to guide health promotion. Health Promotion International. 1996 March 1, 1996;11(1):11-8.
399. EPPI Centre. Quality and relevance appraisal. 2011 [cited 2012 13 February]; Available from: http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=177.
400. Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. Control Clin Trials. 1995;16(1):62-73.
401. Moyer A, Finney JW. Rating methodological quality: Toward improved assessment and investigation. Accountability in Research. 2005;12(4):299-313.
402. Verhagen AP, de Vet HCW, de Bie RA, Boers M, A van den Brandt P. The art of quality assessment of RCTs included in systematic reviews. Journal of clinical epidemiology. 2001;54(7):651-4.

403. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies. . J Clin Epidemiol. 2008;61(4):344-49.
404. Egger M, GD Smith, DG Altman. Systematic reviews in health care: Meta-analysis in context. London: BMJ Books; 2001.
405. Borghouts JAJ, Koes BW, Bouter LM. The clinical course and prognostic factors of non-specific neck pain: a systematic review. Pain. 1998;77(1):1-13.
406. Whiting P, Harbord R, Kleijnen J. Scoring the quality of diagnostic accuracy studies: an example using QUADAS. York: Centre for Reviews and Dissemination, University of York; [cited 2012 11 December]; Available from: https://www.york.ac.uk/inst/crd/Posters/Scoring%20the%20quality%20of%20diagnostic%20accuracy%20studies%20using%20QUADAS%20.pdf.
407. Glasziou P, Irwig L, Bain C, Colditz G. Systematic reviews in health care: A practical guide. Cambridge: Cambridge University Press; 2001.
408. Detsky AS, Naylor CD, O'Rourke K, McGeer AJ, L'Abbe KA. Incorporating variations in the quality of individual randomized trials into meta-analysis. J Clin Epidemiol. 1992;45:255-65.
409. Centre for Reviews and Dissemination, . CRD Report Number 4 (2nd Edition). York: , 2001. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: NHS Centre for Reviews and Dissemination; 2009.
410. Carneiro AV. Critical appraisal of prognostic evidence: practical rules. Rev Port Cardiol. 2002;21:891-900.
411. Centre for Evidence Based Medicine. Critical appraisal of prognostic studies. Oxford: University of Oxford; 2012 [cited 2012 24 February]; Available from: http://www.cebm.net/index.aspx?o=1157.
412. Darzins PJ, Smith BJ, Aust HRMJ, 389–94. How to read a journal article. Medical Jounal of Australia. 1992;157(6):389-94.
413. Katrak P, Bialocerkowski A, Massy-Westropp N, Kumar VS, Grimmer K. A systematic review of the content of critical appraisal tools. BMC Medical Research Methodology. 2004;4(1):22.
414. Greenhalgh T. How to read a paper: Assessing the methodological quality of published papers. BMJ. 1997 1997-08-02 00:00:00;315(7103):305-8.
415. Elwood JM. Critical Appraisal of Epidemiological Studies and Clinical Trials. 2nd ed. Oxford: Oxford University Press; 1998.
416. Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence based medicine. How to practice and teach EBM. London: Churchill Livingstone; 2000.
417. Clarke M, Oxman AD, In Katrak P, Bialocerkowski A, Massy-Westropp N, Kumar VSS, et al. A systematic review of the content of critical appraisal tools. BMC Medical Research Methodology. 2003;4(1):22.
418. Kyzas PA, Loizou KT, Ioannidis JP. Selective reporting biases in cancer prognostic factor studies. J Natl Cancer Inst. 2005;97:1043-55.
419. EPPI Centre. Methods and tools: Quality and relevance appraisal. Social Science Research Unit; 2012 [cited 2012 12 March]; Available from: http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=177.
420. Streiner DL, Norman GR. Health measurement scales: a practical guide to their development and use. Ontario: Oxford University Press; 2008.
421. Groenwold RHH, Rovers MM. The Catch-22 of appraisals on the quality of observational studies. Journal of clinical epidemiology. 2010;63:1059-60.
422. Greenland S. Invited Commentary: A Critical Look at Some Popular Meta-Analytic Methods. American Journal of Epidemiology. 1994 August 1, 1994;140(3):290-6.
423. Keough-Ryan T, Hutchinson T, MacGibbon B, Senecal M. Studies of prognostic factors in end-stage renal disease: an epidemiological and statistical critique. Am J Kidney Dis. 2002(39):1196-205.

424. National Collaborating Centre for Methods and Tools Quality Assessment Tool for Quantitative Studies Method. Hamilton: McMaster University; 2008 [updated 13 April, 2010; cited 2010 23 November]; Available from: http://www.nccmt.ca/registry/view/eng/15.html.
425. National Institute of Clinical Excellence. Methodology checklist: prognostic studies. 2012 [cited 2014 17 December]; Available from: https://www.nice.org.uk/article/pmg6b/chapter/appendix-i-methodology-checklist-prognostic-studies.
426. Booth CM, Li G, Zhang-Salomons J, MacKillop WJ. The impact of socioeconomic status on stage of cancer at diagnosis and survival: A population based study in Ontario, Canada. Cancer. 2010;116(17):4160-67.
427. Castro MAF, Dedivitis RA, Ribeiro KCB. Comorbidity measurement in patients with laryngeal squamous cell carcinoma. ORL. 2007;69(3):146-52.
428. Hathaway B, Johnson JT, Piccirillo JF, Snyderman CH, Wagner RL, Labriola S, et al. Chemoradiation for metastatic SCCA: Role of comorbidity. Laryngoscope. 2001;111(11 I):1893-5.
429. Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. BMJ. 2001 2001-07-07 00:00:00;323(7303):42-6.
430. ISD Scotland. SMR Datasets: Patient identification section. ISD Scotland; 2012 [cited 2012 9 October]; Available from: http://www.datadictionaryadmin.scot.nhs.uk/SMR-Datasets/SMR-Validation-Section/Patient-Identification-Section/Community-Health-Index-Number.asp.
431. University of Dundee. Health Informatics Centre. [cited 2012 24 October]; Available from: http://medicine.dundee.ac.uk/health-informatics-centre.
432. Administrative Data Liaison Service. Scottish Morbidity Database. Edinburgh: Administrative Data Liaison Service; 2015 [cited 2015 1 February]; Available from: http://www.adls.ac.uk/nhs-scotland/scottish-morbidity-database-smr/?detail.
433. Scottish Government. Trend- Scottish Index of Multiple Deprivation. Edinburgh: Scottish Government; 2011 [cited 2012 24 October]; Available from: http://www.scotland.gov.uk/Topics/Statistics/Browse/Social-Welfare/TrendSIMD.
434. Fellegi IP, Sunter AB. A theory for record linkage. Journal of the American Statistical Association. 1969;64:1183-210.
435. Maletic JA, Marcus A. Data cleansing: Beyond intergity analysis. Proceedings of the Conference on Information Quality2000. p. 200-9.
436. Rahm E, Do HH. Data quality: Problems and current approaches. University of Liepzig; 2000 [cited 2013 3 June]; Available from: https://www.informatik.hu-berlin.de/de/forschung/gebiete/ki/mac/lehre/lehrmaterial/Informationsintegration/Rahm00.pdf.
437. Van den Broeck J, Cunningham SA, Eeckles R, Herbst K. Data cleaning: Detection, diagnosing and editing data abnormalities. PLoS Med. 2005;2(10):e267.
438. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical Care. 2005;43(11):1130-9.
439. Sundararajan V, Quan H, Halfon P, Fushimi K, Luthi JC, Burnand B, et al. International Methodology Consortium for Coded Health Information (IMECCHI): Cross-national comparative performance of three versions of the ICD-10 Charlson index. Med Care. 2007;45:1210-5.
440. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Medical Research Methodology. 2011;11.
441. van Walraven C, Austin PC, Jennings A, Quan H, AJ. F. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. Med Care. 2009;47(6):623-33.
442. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. Journal of clinical epidemiology. 1994;47(11):1245-51.

443. Lieffers JR, Baracos VE, Winget M, Fassbender K. A comparison of charlson and elixhauser comorbidity measures to predict colorectal cancer survival using administrative health data. Cancer. 2011;117(9):1957-65.
444. Marventano S, Grosso G, Mistretta A, Bogusz-Czerniewicz M, Ferranti R, Nolfo F, et al. Evaluation of four comorbidity indices and Charlson comorbidity index adjustment for colorectal cancer patients. Int J Colorectal Dis. 2014 2014/09/01;29(9):1159-69.
445. Brewer N, Borman B, Sarfati D, Jeffreys M, Fleming S, Cheng S, et al. Does comorbidity explain the ethnic inequalities in cervical cancer survival in New Zealand? A retrospective cohort study. BMC Cancer. 2011;11(1):132.
446. Xiao H, Tan F, Goovaerts P, Ali A, Adunlin G, Huang Y, et al. Construction of a comorbidity index for prostate cancer patients linking state cancer registry with inpatient and outpatient data. Journal of registry management. 2013;40(4):159-64.
447. Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital Volume and Late Survival After Cancer Surgery. Annals of Surgery. 2007;245(5):777-83.
448. Austin SR, Wong Y, Uzzo RG, Beck JR, Egleston BL. Why Summary Comorbidity Measures Such As the Charlson Comorbidity Index and Elixhauser Score Work. Medical Care. 2013.
449. Green FL, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG. AJCC Cancer Staging Manual. London: American Joint Committee on Cancer; 2002.
450. Holmes J, In Institute of Alcohol Studies. Minimum Unit Pricing & Banning Below Cost Selling: Estimated policy impacts in England 2014/15. 2014 [cited 2014 17 November]; Available from: http://www.ias.org.uk/Alcohol-knowledge-centre/Consumption/Factsheets/A-good-measure-Units-and-drinking-guidelines.aspx.
451. Uzuner O, Goldstein I, Luo Y, Kohane I. Identifying patient smoking status from medical discharge records. J Am Med Inform Assoc. 2008 15(1):14-24.
452. Bohensky MA, Jolley D, Sundararajan V, Evans S, Ibrahim J, Brand C. Development and validation of reporting guidelines for studies involving data linkage. Australian and New Zealand Journal of Public Health. 2011;35(5):486-9.
453. Boing AF, Peres MA, Antunes JLF. Mortality from oral and pharyngeal cancer in Brazil: trends and regional patterns, 1979-2002. Revista Panamericana de Salud Pública. 2006;20:1-8.
454. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity: a critical review of available methods. Journal of clinical epidemiology. 2003;56:221-9.
455. Kaplan MH, Feinstein AR. The importance of classifying initial comorbidity in evaluating the outcome of diabetes mellitus. Journal of Chronic Diseases. 1974;27(7-8):387-404.
456. Paleri V, Narayan R, Wight RG. Descriptive study of the type and severity of decompensation caused by comorbidity in a population of patients with laryngeal squamous cancer. Journal of Laryngology and Otology. 2004;118(7):517-21.
457. Hall W, Ramachandran R, Narayan S, Jani A, Vijayakumar S. An electronic application for rapidly calculating Charlson comorbidity score. BMC Cancer. 2004;4(1):94.
458. National Records of Scotland. Death certificates and coding the cause of death. Edinburgh: National Records of Scotland; 2011 [updated June 2011; cited 2014 3 August]; Available from: http://www.nrscotland.gov.uk/files/statistics/vital-events/about-med-cert-cause-death.pdf.
459. Woodward M. Epidemiology: Study design and data analysis. 3rd ed. Florida: Taylor Francis Group; 2014.
460. Carpenter JR, Kenward MG, Vansteelandt S. A comparison of multiple imputation and doubly robust estimation for analyses with missing data. Journal of the Royal Statistical Society: Series A (Statistics in Society). 2006;169(3):571-84.
461. Uno H, Cai T, Pencina MJ, D'Agostino RB, Wei LJ. On the C-statistics for Evaluating Overall Adequacy of Risk Prediction Procedures with Censored Survival Data. Statistics in Medicine. 2011;30(10):1105-17.
462. Akaike H, In:Petrov BN, Csaki F, eds. Information theory and an extension of the maximum likelihood principle. Budapest: 2nd International Symposium on Information Theory; 1973.

463. Burnham KP, Anderson DR. Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach. Fort Collins: Springer Science & Business Media; 2007.
464. Chen AY, Pavluck A, Halpern M, Ward E. Impact of treating facilities' volume on survival for early-stage laryngeal cancer. Head & Neck. 2009 Sep;31(9):1137-43.
465. Luke CG, Yeoh E, Roder DM. Exploring trends in laryngeal cancer incidence, mortality and survival: implications for research and cancer control. Asian Pac J Cancer Prev. 2008 Jul-Sep;9(3):397-402.
466. Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP. Trends in incidence and prognosis for head and neck cancer in the United States: A site-specific analysis of the SEER database. International Journal of Cancer. 2005;114(5):806-16.
467. Allen NE, Beral V, Casabonne D, Kan SW, Reeves GK, Brown A, et al. Moderate alcohol intake and cancer incidence in women. Journal of the National Cancer Institute. 2009 Mar 4;101(5):296-305.
468. Burger M, Bronstrup A, Pietrzik K. Derivation of tolerable upper alcohol intake levels in Germany: a systematic review of risks and benefits of moderate alcohol consumption. Preventive Medicine. 2004 Jul;39(1):111-27.
469. Franceschi S, Talamini R, Barra S, BarÃ³n AE, Negri E, Bidoli E, et al. Smoking and Drinking in Relation to Cancers of the Oral Cavity, Pharynx, Larynx, and Esophagus in Northern Italy. Cancer Research. 1990 October 15, 1990;50(20):6502-7.
470. Freedman ND, Schatzkin A, Leitzmann MF, Hollenbeck AR, Abnet CC. Alcohol and head and neck cancer risk in a prospective study. British Journal of Cancer. 2007;96(9):1469-74.
471. Macfarlane G. Alcohol, tobacco, diet and the risk of oral cancer: a pooled analysis of three case-control studies. Eur J Cancer B Oral Oncol. 1995;31B(3):181 - 7.
472. Boing AF, Antunes JLF, de Carvalho MB, de Gois JF, Kowalski LP, Michaluart P, et al. How much do smoking and alcohol consumption explain socioeconomic inequalities in head and neck cancer risk? Journal of Epidemiology and Community Health. 2011 Aug;65(8):709-14.
473. Bosetti C, Gallus S, Peto R, Negri E, Talamini R, Tavani A, et al. Tobacco smoking, smoking cessation, and cumulative risk of upper aerodigestive tract cancers. American Journal of Epidemiology. 2008 Feb 15;167(4):468-73.
474. Brennan J. Association between cigarette smoking and mutation of the p53 gene in squamous-cell carcinoma of the head and neck. N Engl J Med. 1995;332(11):712 - 7.
475. Chodorowski Z, Stankiewicz C, Sein Anand J, Wisniewski M, Sierszen W. Tobacco smoking and multiple primary cancers. Przegl Lek. 2007;64(4-5):374-5.
476. Clark JR, McCluskey SA, Hall F, Lipa J, Neligan P, Brown D, et al. Predictors of morbidity following free flap reconstruction for cancer of the head and neck. Head & Neck. 2007 Dec;29(12):1090-101.
477. Doll R PR, Boreham J, et al. Mortality in relation to smoking: 50 years observations on British doctors. Br J Cancer. 2005;92:426-9.
478. Granata R, Miceli R, Orlandi E, Perrone F, Cortelazzi B, Franceschini M, et al. Tumor stage, human papillomavirus and smoking status affect the survival of patients with oropharyngeal cancer: an Italian validation study. Annals of Oncology. 2012 July 1, 2012;23(7):1832-7.
479. Herold C, Gohritz A, Meyer-Marcotty M, Steiert A, Jokuszies A, Vaske B, et al. Is There an Association between Comorbidities and the Outcome of Microvascular Free Tissue Transfer? Journal of Reconstructive Microsurgery. 2011 Feb;27(2):127-32.
480. Hoff CM, Grau C, Overgaard J. Effect of smoking on oxygen delivery and outcome in patients treated with radiotherapy for head and neck squamous cell carcinoma – A prospective study. Radiotherapy and Oncology.103(1):38-44.
481. Park SM, Lim MK, Shin SA, Yun YH. Impact of prediagnosis smoking, alcohol, obesity, and insulin resistance on survival in male cancer patients: National Health Insurance Corporation Study. Journal of Clinical Oncology. 2006 Nov 1;24(31):5017-24.

482. Pednekar MS, Gupta PC, Yeole BB, Hebert JR. Association of tobacco habits, including bidi smoking, with overall and site-specific cancer incidence: results from the Mumbai cohort study. Cancer Causes & Control. 2011 Jun;22(6):859-68.
483. Anscher MS, Gold DT. Literacy and laryngectomy: how should one treat head and neck cancer in patients who cannot read or write? Southern Medical Journal. 1991 Feb;84(2):209-13.
484. Bouchardy C, Parkin DM, Khlat M, Mirra AP, Kogevinas M, De Lima FD, et al. Education and mortality from cancer in Sao Paulo, Brazil. Annals of Epidemiology. 1993 Jan;3(1):64-70.
485. Fernandez E, Borrell C. Cancer mortality by educational level in the city of Barcelona. British Journal of Cancer. 1999 Feb;79(3-4):684-9.
486. Brusselaers N, Mattsson F, Lindblad M, Lagergren J. Association between education level and prognosis after esophageal cancer surgery: A Swedish population-based cohort study. PLoS ONE. 2015;10(3).
487. Danker H, Keszte J, Singer S, Thoma J, Taschner R, Brahler E, et al. Alcohol consumption after laryngectomy. Clinical Otolaryngology. 2011 Aug;36(4):336-44.
488. Datema FR, Poldermans D, Baatenburg de Jong RJ. Incidence and prediction of major cardiovascular complications in head and neck surgery. Head & Neck. 2010 Nov;32(11):1485-93.
489. Mayne ST, Cartmel B, Kirsh V, Goodwin WJ. Alcohol and Tobacco Use Pre- and Post-Diagnosis and Survival In a Cohort of Patients With Early Stage Cancers of the Oral Cavity, Pharynx And Larynx. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2009;18(12):3368-74.
490. Potash AE, Karnell LH, Christensen AJ, Vander Weg MW, Funk GF. Continued alcohol use in patients with head and neck cancer. Head and Neck. 2010 July;32(7):905-12.
491. Tramacere I, Negri E, Bagnardi V, Garavello W, Rota M, Scotti L, et al. A meta-analysis of alcohol drinking and oral and pharyngeal cancers. Part 1: Overall results and dose-risk relation. Oral Oncology.46(7):497-503.
492. Turati F, Garavello W, Tramacere I, Bagnardi V, Rota M, Scotti L, et al. A meta-analysis of alcohol drinking and oral and pharyngeal cancers. Part 2. Results by subsites. Oral Oncol. 2010;46:720-6.
493. Gutacker N, Bloor K, Cookson R. Comparing the performance of the Charlson/Deyo and Elixhauser comorbidity measures across five European countries and three conditions2015.
494. Paleri V, Wight RG, Davies GR. Impact of comorbidity on the outcome of laryngeal squamous cancer. Head & Neck. 2003 Dec;25(12):1019-26.
495. Teymoortash A, Halmos G, Silver C, Strojan P, Haigentz M, Jr., Rinaldo A, et al. On the need for comprehensive assessment of impact of comorbidity in elderly patients with head and neck cancer. European Archives of Oto-Rhino-Laryngology. 2014 2014/10/01;271(10):2597-600.
496. Ankola AA, Smith RV, Burk RD, Prystowsky MB, Sarta C, Schlecht NF. Comorbidity, human papillomavirus infection and head and neck cancer survival in an ethnically diverse population. Oral Oncology. 2013;49(9):911-7.
497. Omura G, Ando M, Saito Y, Kobayashi K, Yamasoba T, Asakage T. Comorbidities Predict Poor Prognosis for Advanced Head and Neck Cancer Patients Treated with Major Surgery. Head & Neck. 2014:n/a-n/a.
498. Sesterhenn AM, Teymoortash A, Folz BJ, Werner JA. Head and neck cancer in the elderly: a cohort study in 40 patients. Acta Oncologica. 2005;44(1):59-64.
499. van der Schroeff MP, Derks W, Hordijk GJ, de Leeuw RJ. The effect of age on survival and quality of life in elderly head and neck cancer patients: a long-term prospective study. European Archives of Oto-Rhino-Laryngology. 2007 Apr;264(4):415-22.
500. Ribeiro K, Kowalski LP, Md. Impact of comorbidity, symptoms, and patients' characteristics on the prognosis of oral carcinomas. Archives of Otolaryngology - Head & Neck Surgery. 2000;126(9):1079-85.

501. Yancik R, Wesley MN, Ries LG, Havlik RJ, Edwards BK, Yates JW. EFfect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA. 2001;285(7):885-92.
502. Satariano WA. Comorbidity and functional status in older women with breast cancer: implications for screening, treatment, and prognosis. Journal of gerontology. 1992;47 Spec No:24-31.
503. Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J. The Impact of Co-morbidity on Life Expectancy Among Men with Localized Prostate Cancer. The Journal of Urology. 1996;156(1):127-32.
504. Clemens JD, Feinstein AR, Holabird N, Cartwright S. A new clinical-anatomic staging system for evaluating prognosis and treatment of prostatic cancer. Journal of Chronic Diseases. 1986;39(11):913-28.
505. Yancik R, Wesley MN, Ries LAG, Havlik RJ, Long S, Edwards BK, et al. Comorbidity and age as predicctors of risk for early mortality of male and female colon carcinoma patients. Cancer. 1998;84:2123-34.
506. Jalisi S, Bearelly S, Abdillahi A, Truong MT. Construction of a Comorbidity Index for Prostate Cancer Patients Linking State Cancer Registry with Inpatient and Outpatient Data. Laryngoscope. 2013;123:689-98.
507. Southern DA, Quan H, Ghali WA. Comparison of the Elixhauser and Charlson/Deyo methods of comorbidity measurement in administrative data. Med Care. 2004;42:355-60.
508. Menendez ME, Neuhaus V, van Dijk CN, Ring D. The Elixhauser comorbidity method outperforms the Charlson index in predicting inpatient death after orthopaedic surgery. Clinical Orthopaedics and Related Research. 2014;472:2878-86.
509. Chu Y-T, Ng Y-Y, Wu S-C. Comparison of different comorbidity measures for use with administrative data in predicting short- and long-term mortality. Bmc Health Services Research. 2010;10:140-.
510. Li B, Evans D, Faris P, Dean S, Quan H. Risk adjustment performance of Charlson and Elixhauser comorbidities in ICD-9 and ICD-10 administrative databases. Bmc Health Services Research. 2008;14(8):12.
511. Thompson NR, Fan Y, Dalton JE, Jehi L, Rosenbaum BP, Vadera S, et al. A New Elixhauser-based Comorbidity Summary Measure to Predict In-Hospital Mortality. Medical Care. 2015;53(4):374-9.
512. Chu KP, Shema SJ, Wu S, Gomez SL, Chang ET, Le Q. Survival from head and neck cancers based on socioeconomic status in Asians. Journal of Clinical Oncology Conference. 2010;28(15 SUPPL. 1).
513. Schleiffarth JR, Charlton M, Pagedar NA. Head and Neck Cancer Mortality, Socioeconomic Status, and Distribution of Otolaryngologists. Otolaryngology -- Head and Neck Surgery. 2013 September 1, 2013;149(2 suppl):P151-P2.
514. Subramanian S, Chen A. Treatment patterns and survival among low-income medicaid patients with head and neck cancer. JAMA Otolaryngology–Head & Neck Surgery. 2013;139(5):489-95.
515. Brown LM, Check DP, Devesa SS. Oropharyngeal cancer incidence trends: diminishing racial disparities. Cancer Causes & Control. [ ]. 2011 May;22(5):753-63.
516. Amarasinghe HK, Johnson NW, Lalloo R, Kumaraarachchi M, Warnakulasuriya S. Derivation and validation of a risk-factor model for detection of oral potentially malignant disorders in populations with high prevalence. British Journal of Cancer. 2010 Jul 27;103(3):303-9.
517. Peto R, Lopez AD, Boreham J, Thun M. Mortality from smoking in developed countries 1950-2007: Scotland (incl 2004): Scottish Public Health Observatory; 2006. Available from: http://www.scotpho.org.uk/nmsruntime/saveasdialog.asp?lID=3904&sID=3256.
518. Petti S, Scully C. Determinants of oral cancer at the national level: just a question of smoking and alcohol drinking prevalence? Odontology. 2010 Jul;98(2):144-52.

519. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: An emerging epidemic of human papillomavirus-associated cancers? Cancer. 2007 01 Oct;110(7):1429-35.
520. Burzynski NJ, Firriolo FJ, Butters JM, Sorrell CL. Evaluation of oral cancer screening. J Cancer Educ. 1997;12(2):95-9.
521. Cruz GD, Le Geros RZ, Ostroff JS, Hay JL, Kenigsberg H, Franklin DM. Oral cancer knowledge, risk factors and characteristics of subjects in a large oral cancer screening program. J Am Dent Assoc. 2002 Aug;133(8):1064-71; quiz 94.
522. Amir Z, Kwan SY, Landes D, Feber T, Williams SA. Diagnostic delays in head and neck cancers. European Journal of Cancer Care. 1999 Dec;8(4):198-203.
523. Epstein JB, Gorsky M, Cabay RJ, Day T, Gonsalves W. Screening for and diagnosis of oral premalignant lesions and oropharyngeal squamous cell carcinoma - Role of primary care physicians. Canadian Family Physician. 2008 Jun;54(6):870-5.
524. Patel UA, Lynn-Macrae A, Rosen F, Holloway N, Kern R. Advanced stage of head and neck cancer at a tertiary-care county hospital. Laryngoscope. 2006 Aug;116(8):1473-7.
525. Round A WD. Cancer diagnosis in primary care. Hamilton W PT, editor. Edinburgh: Churchill Livingstone; 2007.
526. Fakhry C, D'Souza G. Discussing the diagnosis of HPV-OSCC: Common questions and answers. Oral Oncology. 2013;49(9):863-71.
527. Jiang H, Lin P-F. Human papillomavirus infection a favorable prognostic factor in laryngeal squamous cell carcinoma is associated with the expression of proliferating cell nuclear antigen. Pakistan Journal of Medical Sciences. 2013 Sep-Oct;29(5):1173-7.
528. Posner MR, Lorch JH, Goloubeva O, Tan M, Schumaker LM, Sarlis NJ, et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. Annals of Oncology. 2011;22(5):1071-7.
529. Janssen-Heijnen ML, Gondos A, Bray F, Hakulinen T, Brewster DH, Brenner H, et al. Clinical relevance of conditional survival of cancer patients in Europe: age-specific analyses of 13 cancers. J Clin Oncol. 2010;28:2520-8.
530. Boeje CR, Overgaard J. Comorbidity in radiotherapy-treated head and neck cancer - The impact of individual comorbidities on survival. European Journal of Cancer. 2011;47:S546.
531. Comorbidities affect survival of patients with head, neck cancer. J Am Dent Assoc. 2009 Feb;140(2):152.
532. Albertsen PC, Moore DF, Shih W, Lin Y, Li H, Lu-Yao GL. Impact of Comorbidity on Survival Among Men With Localized Prostate Cancer. Journal of Clinical Oncology. 2011;29(10):1335-41.
533. Battafarano RJ, Piccirillo JF, Meyers BF, Hsu HS, Guthrie TJ, Cooper JD, et al. Impact of comorbidity on survival after surgical resection in patients with stage I non-small cell lung cancer. Journal of Thoracic and Cardiovascular Surgery. 2002 Feb;123(2):280-7.
534. Polednak AP. Poverty, Comorbidity, and Survival of Colorectal Cancer Patients Diagnosed in Connecticut. Journal of Health Care for the Poor and Underserved. 2001;12(3):302-10.
535. Beddhu S, Bruns FJ, Saul M, Seddon P, Zeidel ML. A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. American Journal of Medicine. 2000;108(8):609-13.
536. Houterman S, Janssen-Heijen MLG, Verheij CDGW, Louwman WJ, Vreugdenhil G, van der Sangen MJC, et al. Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. British Journal of Cancer. 2004;90:2332-7.
537. Fleming ST, Pursley HG, Newman B, Pavlov D, Chen K. Comorbidity as a predictor of stage of illness for patients with breast cancer. Medical Care. 2005;43(2):132-40.
538. Janssen-Heijen ML, von Spronsen DJ, Lemmens VE, et al. A population-based study of severity of comorbidity among patients with non-Hodgkins lymphoma: prognostic impact independent of International Prognostic Index. Br J Haematol. 2005;129:597-606.

539. Gossage JA, Forshaw MJ, Khan AA, Mak V, Moller H, Mason RC. The effect of economic deprivation on oesophageal and gastric cancer in a UK cancer network. Int J Clin Prac. 2009;63(6):859-64.
540. Dutta Roy S, Philip J, Javle P. Trends in prostate cancer incidence and survival in various socioeconomic classes: a population-based study. International journal of urology : official journal of the Japanese Urological Association. 2006;13(10):1364.
541. Stott P. Upper gastrointestinal cancer and economic deprivation - data from a London (UK) Cancer Network. International Journal of Clinical Practice. 2009;63(6):835-7.
542. Wu CC, Hsu TW, Chang CM, Yu CH, Wang YF, Lee CC. The effect of individual and neighborhood socioeconomic status on gastric cancer survival. PLoS ONE. 2014;9(2).
543. Sharpe KH, McMahon AD, McClements P, Watling C, Brewster DH, Conway DI. Socioeconomic inequalities in incidence of lung and upper aero-digestive tract cancer by age, tumour subtype and sex: A population-based study in Scotland (2000–2007). Cancer Epidemiology.36(3):e164-e70.
544. Bradley CJ, Given CW, Roberts C. Race, socioeconomic status, and breast cancer treatment and survival. J Natl Cancer Inst. 2002;94(7):490-6.
545. Anderson ZJ, Lassen CF, Clemmensen IH. Social inequality and incidence of and survival from cancers of the mouth, pharynx and larynx in a population-based study in Denmark, 1994-2003. Eur J Cancer. 2008;44:1950-61.
546. Leigh Y, Seagroatt V, Goldacre M, McCulloch P. Impact of socio-economic deprivation on death rates after surgery for upper gastrointestinal tract cancer. British Journal of Cancer. 2006;95(7):940-3.
547. Piccirillo JF. Impact of comorbidity and symptoms on the prognosis of patients with oral carcinoma. Arch Otolaryngol Head Neck Surg. [Comment

Editorial]. 2000 Sep;126(9):1086-8.
548. Luthi J-C, Troillet N, Eisenring M-C, Sax H, Burnand B, Quan H, et al. Administrative data outperformed single-day chart review for comorbidity measure2007.
549. Kieszak SM, Flanders WD, Kosinski AS, Shipp CC, Karp H. A Comparison of the Charlson Comorbidity Index Derived from Medical Record Data and Administrative Billing Data. Journal of Clinical Epidemiology.52(2):137-42.
550. Needham DM, Scales DC, Laupacis A, Pronovost PJ. A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. Journal of Critical Care.20(1):12-9.
551. Smith JP. The impact of socioeconomic status on health over the lifecourse. J Hum Resour. 2007;42:739-64.
552. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls2009.
553. Benard VB, Johnson CJ, Thompson TD, Roland KB, Lai SM, Cokkinides V, et al. Examining the Association Between Socioeconomic Status and Potential Human Papillomavirus-associated Cancers. Cancer. 2008 Nov;113(10):2910-8.
554. Johnston MC, Marks A, Crilly MA, Prescott GJ, Robertson LM, Black C. Charlson index scores from administrative data and case-note review compared favourably in a renal disease cohort2015.
555. Leal JR, Laupland KB. Validity of ascertainment of co-morbid illness using administrative databases: a systematic review. Clin Microbiol Infect. 2010;16:715-21.
556. Catto S, Gibbs D. How much are people in Scotland really drinking? A review of data from Scotland's routine national surveys, 2008: Scottish Public Health Observatoy2008 26 May 2008.
557. Sharabiani M, Aylin P, Bottle A. Systematic review of comorbidity indices for administrative data. Medical Care. 2012;50(12):1109-18.
558. Dronkers E, Mes S, Wieringa M, van der Schroeff M, Baatenburg de Jong R. Noncompliance to guidelines in head and neck cancer treatment; associated factors for both patient and physician. BMC Cancer. 2015;15(1):515.

559. Derks W, De Leeuw R, Winnubst J, Hordijk GJ. Elderly patients with head and neck cancer: Physical, social and psychological aspects after 1 year. Acta Oto-Laryngologica. 2004 May;124(4):509-14.
560. Joseph K, Vrouwe S, Kamruzzaman A, Balbaid A, Fenton D, Berendt R, et al. Outcome analysis of breast cancer patients who declined evidence-based treatment. World Journal of Surgical Oncology. 2012;10(1):118.
561. Ghali WA, Hall RE, Rosen AK, Ash AS, Moskowitz MA. Searching for an improved clinical comorbidity index for use with ICD-9-CM administrative data. Journal of Clinical Epidemiology.49(3):273-8.
562. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies using administrative databases. Int J Epidemiol. 2000;29(5):891-8.
563. Piccirillo JF. Inclusion of comorbidity in a staging system for head and neck cancer. Oncology (Williston). 1995 Sep;9(9):831-6; discussion 41, 45-8.
564. Baijal G, Gupta T, Hotwani C, Laskar SG, Budrukkar A, Murthy V, et al. Impact of comorbidity on therapeutic decision-making in head and neck cancer: Audit from a comprehensive cancer center in India. Head & Neck. 2012;34(9):1251-4.
565. Bonavita V, De Simone R. Towards a definition of comorbidity in the light of clinical complexity. Neurological Sciences. 2008;29(1 Suppl):99-102.
566. Molto A, Dougados M. Comorbidity indices. Clinical and Experimental Rheumatolology. 2014;32(Suppl. 85):S131-S4.
567. Grundy E, Holt G. The socioeconomic status of older adults: How should we measure it in studies of health inequalities? Journal of Epidemiology and Community Health. 2001 December 1, 2001;55(12):895-904.
568. Macleod U, Mitchell E, Black M, Spence G. Comorbidity and socioeconomic deprivation: an observational study of the prevalence of comorbidity in general practice. European Journal of General Practice. 2004;10(1):24-6.
569. Sloggett A, Joshi H. Higher mortality in deprived areas: community or personal disadvantage? BMJ : British Medical Journal. 1994;309(6967):1470-4.
570. Do DP, Finch BK. The Link between Neighborhood Poverty and Health: Context or Composition? American Journal of Epidemiology. 2008 September 15, 2008;168(6):611-9.
571. Antonovsky A IIPHP, ,. Framework. International Public Health Partnership; 2010 [cited 2015 10 August]; Available from: http://iph-partnership.org/index.php?title=1.2._Framework.
572. Eriksson M, Lindström B. Antonovsky's sense of coherence scale and the relation with health: a systematic review. Journal of Epidemiology and Community Health. 2006;60(5):376-81.
573. Antonovsky A. Unraveling the mystery of health. How people manage stress and stay well. San Francisco: Jossey-Bass; 1987.
574. Vartanian JG, Carvalho AL, Toyota J, Giacometti Kowalski IS, Kowalski LP. Socioeconomic effects of and risk factors for disability in long-term survivors of head and neck cancer. Archives of Otolaryngology - Head and Neck Surgery. 2006 Jan;132(1):32-5.
575. Paleri V, Wight RG. Applicability of the adult comorbidity evaluation - 27 and the Charlson indexes to assess comorbidity by notes extraction in a cohort of United Kingdom patients with head and neck cancer: a retrospective study. Journal of Laryngology & Otology. 2002 Mar;116(3):200-5.
576. Rogers SN, Aziz A, Lowe D, Husband DJ. Feasibility study of the retrospective use of the Adult Comorbidity Evaluation index (ACE-27) in patients with cancer of the head and neck who had radiotherapy. British Journal of Oral and Maxillofacial Surgery. 2006;44(4):283-8.
577. Jones AS, Ravi M, Stell PM. The treatment of primary recurrence following laryngectomy for laryngeal carcinoma. Journal of Laryngology & Otology. 1993 Jul;107(7):611-3.
578. Franco EL, Kowalski LP, Kanda JL. Risk factors for second cancers of the upper respiratory and digestive systems: a case-control study. Journal of clinical epidemiology. 1991;44(7):615-25.
579. Bossetti C, Franceschi S, Negri E, Talamini R, Tomei F, La Vecchia C. Changing socioeconomic correlates fo cancers of the upper digestive tract. Annals of Oncology. 2001;12:327-30.

580. Powles T, Powles J, Nelson M, Sandison A, Peston D, Buchannan J, et al. Head and neck cancer in patients with human immunodeficiency virus-1 infection: incidence, outcome and association with Epstein-Barr virus. Journal of Laryngology & Otology. 2004;118(3):207-12.
581. Kutler DI, Auerbach AD, Satagopan J, Giampietro PF, Batish SD, Huvos AG, et al. High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia. Arch Otolaryngol Head Neck Surg. 2003 Jan;129(1):106-12.
582. Kuo HC, Yang YH, Ho PS, Chang LT. Risk of comorbidity on head and neck cancer treatment: A population-based study. Oral Oncology. 2011;47:S93.
583. Singh B, Bhaya M, Zimbler M, Stern J, Roland JT, Rosenfeld RM, et al. Impact of comorbidity on outcome of young patients with head and neck squamous cell carcinoma. Head and Neck. 1997;20(1):1-7.

Moose Guidelines Checklist

Table 81 MOOSE Guidelines Checklist

	Reported on page	Comments
Reporting of background should include		
Problem definition	32	Described in the background text
Hypothesis statement	33	
Description of study outcomes	36	
Type of exposure or intervention used		N/A
Type of study designs used	34-35	Listed in inclusion/exclusion criteria
Study population	34	
Reporting of search strategy should include		
Qualifications of searchers (e.g. librarians and investigators)	37	1st reviewer with checking by Librarian & Systematic reviewer
Search strategy, including time period used in the synthesis and key words	263-277	Appendix A3
Effort to include all available studies, including contact with authors		Not conducted as adequate data available in primary studies
Databases and registries searched	37	Cochrane Library, York CRD, Joanna Briggs Institute Library of Systematic Reviews, MEDLINE and the Database of Abstracts and Reviews of Effects
Search software used, name and version, including special features used (e.g. explosion)	264-278	MEDLINE, MeSH, explosion and keyword search, proximal and adjective search EMBASE, map terms key words and explosion ISI Web of Science – key words LILACS – key word search SciELO – key word search CINAHL – Medical headings, key word search
Use of hand searching (e.g. reference lists of obtained articles)	38	Described
List of citations located and those excluded, including justification	279	Appendix A4
Method of addressing articles published in languages other	38	Translation available for

than English		articles in Spanish, German, Portuguese and Polish
Method of handling abstracts and unpublished studies		N/A
Description of any contact with authors		None required as adequate data available
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	34-35	Inclusion/exclusion criteria
Rationale for the selection and coding of data (e.g. sound clinical principles or convenience)	43	Assessment of study eligibility
Documentation of how data were classified and coded (e.g. multiple raters, blinding and interrater reliability)	39	First 2 reviewers selected articles for inclusion. Lack of consensus resolved by 3rd reviewer
Assessment of confounding (e.g. comparability of cases and controls in studies where appropriate)	42-43	QA tool developed to account for this
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	42-43	QA tool developed to account for this
Assessment of heterogeneity	48-49	Results grouped as comorbidity + SES, comorbidity only, SES only
Description of statistical methods (e.g. complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	50-51	Full description of meta-analytic methods given
Provision of appropriate tables and graphics	52-61	Parameter estimate tables and forest plots
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	52-61	
Table giving descriptive information for each study included	292-314	Appendix A5 Data abstraction tables
Results of sensitivity testing (e.g. subgroup analysis)	292-314	Appendix A5 Data abstraction tables
Indication of statistical uncertainty of findings		N/A
Reporting of discussion should include		
Quantitative assessment of bias (e.g. publication bias)	74	
Justification for exclusion (e.g. exclusion of non-English language citations)	74	
Assessment of quality of included studies	42-43	QA tool developed for study
Reporting of conclusions should include		
Consideration of alternative explanations for observed results		N/A
Generalization of the conclusions (e.g. appropriate for the data presented and within the domain of the literature	75	

review)		
Guidelines for future research	75	
Disclosure of funding source		

Systematic review protocol

Title of systematic review: The effect of comorbidity and deprivation on cancer presentation in the community: Head and neck cancer systematic review.

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Background

A global review of cancer has shown an inverse relationship between cancer incidence and survival and socioeconomic factors. Although this does not apply to all known cancer sites, the existing differences in survival are still a cause for concern. Previous reviews have also identified this association. [1; 2; 3] Another important determinant for cancer survival that has been identified is the presence of a pre-existing medical condition or comorbidity. Rosenbaum describes a comorbidities as, 'chronic illnesses that exist simultaneously with and usually independent of another medical condition, in this case cancer'. [4] There is some evidence that having one or more of these pre-existing medical conditions may affect the impact and severity of the cancer thereby affecting outcomes/ prognosis. [5]

As pointed out by Yancik *et al*, cancer incidence increases exponentially with increasing age but this advancement in age also brings with it an increased susceptibility to health problems. [7]. Although survival trends available from ISD Scotland [7] show large absolute increases for breast, colorectal and prostate cancer on an ecological level, it is unknown how these statistics relate to individual factors such as level of deprivation and comorbidity status.

Towards a Healthier Scotland targeted the reduction of health inequalities as a key priority suggesting that research should focus on the causes of these inequalities and the practical means to tackle them. [8] The aim of the Scottish Executive at this time was to reduce cancer mortality by 20% which was implemented through a colorectal demonstration project. Despite the advantages of screening such as early disease detection and treatment, screening is not the only solution to the significant, public health, medical and policy challenges of cancer. There are other important variables to consider such as deprivation (socioeconomic status) and comorbidity. As the effect of comorbidity and social deprivation has not been extensively researched for the 4 cancers, namely head and neck, colorectal, breast and prostate; this systematic review will attempt to investigate this. [9; 10]

From previous research it was identified that low socioeconomic status was linked to worse prognosis and that the same relationship existed for comorbidity and outcomes. What is as yet uncertain is whether being from a deprived background increases the likelihood of having one or more comorbidities or whether both deprivation and comorbidity have an independent effect on cancer outcomes. It will be interesting to measure this effect as either confounding or effect modification of one risk factor over another.

Objectives

The primary objective of this review is to establish what effect comorbidity and deprivation have on patient survival in 4 cancers namely, breast, colorectal, prostate and head and neck. The specific questions are:

- Do comorbidities and socioeconomic status have an independent effect from each other on survival following cancer?
- What is the prognosis of these patients dependent on cancer stage at presentation?

Criteria for considering studies for this review

Types of studies

The review will consider studies that focus on the outcomes of patients diagnosed with any of the following cancers with concurrent comorbidities and socioeconomic status. Studies that compare cancer patients based on socioeconomic status and/or pre-existing medical conditions will also be considered.

Studies reviewing other cancers apart from the 4 cancers under review will be excluded. In the absence of research studies, other forms of evidence such as text and opinion papers will be considered for inclusion in a narrative summary.

Types of participants

The participants of interest are adult patients with a diagnosis of cancers of the breast, colorectal, head and neck or prostate gland. The age will be restricted to exclude patients with childhood cancers with no upper limit on the age as comorbidities are more likely to occur with more advanced age. Also it is envisaged that the impact of deprivation will be difficult to measure in a younger population bearing in mind that these cancers usually occur after the 5th decade of life.

The outcome of interest

This is the survival rates of cancer patients with pre-existing medical conditions from deprived backgrounds. This will be analysed based on all cause mortality versus cancer specific mortality to measure the true effect of these variables on survival.

References:

1. Macleod U, Ross S, Gillis C, McConnachie A, Twelves C, Watt GC. Socio-economic deprivation and stage of disease at presentation in women with breast cancer. *Annals of Oncology* 2000; 11(1):105-7.

2. Thomson CS, Hole DJ, Twelves CJ, Brewster DH, Black RJ, Scottish Cancer Therapy N. Prognostic factors in women with breast cancer: distribution by socioeconomic status and effect on differences in survival. *Journal of Epidemiology & Community Health* 2001; 55(5):308-15.

3. Bradley CJ, Given CW, Roberts C. Race, socioeconomic status, and breast cancer treatment and survival. *J Natl Cancer Inst* 2002; 94(7):490-6, 2002 Apr 3.

4. Henley NC, Hole DJ, Kesson E, Burns HJ, George WD, Cooke TG, et al. Does deprivation affect breast cancer management? *British Journal of Cancer* 2005; 92(4):631-3.

5. Macleod U, Ross S, Twelves C, George WD, Gillis C, Watt GC. Primary and secondary care management of women with early breast cancer from affluent and deprived areas: retrospective review of hospital and general practice records. *BMJ* 2000; 320(7247):1442-5.

6. Ogle KS, Swanson GM, Woods N, Azzouz F. Cancer and comorbidity: redefining chronic diseases. *Cancer* 2000; 88(3):653-63.

7. Houterman S, Janssen-Heijnen ML, Verheij CD, Louwman WJ, Vreugdenhil G, van der Sangen MJ, et al. Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. *British Journal of Cancer* 2004; 90(12):2332-7.

8. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL, Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA* 2004; 291(20):2441-7.

9. Fleming ST, Pursley HG, Newman B, Pavlov D, Chen K. Comorbidity as a predictor of stage of illness for patients with breast cancer. *Medical Care* 2005; 43(2):132-40.

10. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. *European Journal of Cancer* 2005; 41(5):779-85.

11. Munro AJ, Bentley AHM. Deprivation, comorbidity and survival in a cohort of patients with colorectal cancer. *European Journal of Cancer Care* 2004; 13: 254–262.

12. Munro AJ. Deprivation and survival in patients with cancer: we know so much, but do so little. *Lancet Oncology* 2005; 6(12):912-913.

13. McCowan C, Shearer J, Donnan PT, Dewar JA, Crilly M, Thompson AM, Fahey T P. Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. *British Journal of Cancer* 2008 99 1763-68.

14. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity: a critical review of available methods. *Journal of Clinical Epidemiology* 2003; 56(3):221-9.

15. Perkins AJ, Kroenke K, Unutzer J, Katon W, Williams JW, Hope C, et al. Common comorbidity scales were similar in their ability to predict health care costs and mortality. *Journal of Clinical Epidemiology* 2004; 57(10):1040-8.

16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases* 1987; 40(5):373-83.

17. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of Clinical Epidemiology* 1992; 45(6):613-9.

18. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *Journal of Clinical Epidemiology* 2004; 57(12):1288-94.

Search strategy for identification of studies (Appendix I)

Prior to commencing the systematic review process, databases were searched to verify whether a systematic review on this subject had been previously conducted. The search was done in the following: The Cochrane Library, Joanna Briggs Institute Library of Systematic Reviews, MEDLINE and the Database of Abstracts and Reviews of Effects (DARE) were searched and no systematic reviews were found on this topic.

It is considered prudent to approach the literature search using a step-wise method involving three steps. The first step involves an initial limited search of MEDLINE and Cancerlit to help identify relevant keywords contained in the title and abstract and subject descriptors. The second step will involve a comprehensive and exhaustive search using all identified keywords and index terms specific to each included database and internet search engines. Thirdly, the reference list of all included research papers will be searched for additional studies while relevant journals will also be hand searched.

Databases to be searched will be:

1. MEDLINE

2. ISI Web of science

3. CINAHL

4. LILACS

5. Ovid databases, e.g. Embase, BNI

7. SCIelo

Methods

Assessment of methodological quality

This will be conducted using the Effective Public Health Practice Quality Assessment Tool for observational studies. All relevant articles of observational studies will be independently appraised by both the researcher and supervisor for methodological quality. If any disagreements are evident, the article in question will be discussed but if different opinions prevail it will be passed on to a third reviewer who is the researcher's associate supervisor.

Data extraction

This will be done using a standard format adapted from a previously used data abstraction sheet. [3] The information to be collected will include the following:

- Ref number
- First author + year; Title of article; Setting for the study
- Cancer anatomic site and stage; ICD-10 codes
- Data analysis methods
- Measure of comorbidity/ socioeconomic status
- Description of results

Data synthesis

Dependent on the outcomes of the studies, a meta-analysis will be attempted, but this will hinge on homogeneity of studies under review. Where a meta-analysis is not possible, a narrative summary of findings will be conducted.

Literature search strategies

A3.1. MEDLINE Search

1 exp "head and neck neoplasms"/ or exp facial neoplasms/ or exp mouth neoplasms/ or exp otorhinolaryngologic neoplasms/ or exp tracheal neoplasms/ (385001)

2 exp "head and neck neoplasms"/ or facial neoplasms/ or mouth neoplasms/ or otorhinolaryngologic neoplasms/ or tracheal neoplasms/ (379228)

3 (neck adj5 neoplasm).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (1605)

4 (head adj5 neoplasm).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (775)

5 (head and neck neoplas*).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (34011)

6 (head and neck cancer).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (34652)

7 (head adj5 cancer).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (38413)

8 (head adj5 tum*r).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (18658)

9 (head adj5 tum?r).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (17829)

10 ((head or neck or oral cavity or pharyng* or hypopharyng*) adj5 cancer).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (44650)

11 ((head or neck or oral cavit* or pharyng* or hypopharyng*) adj5 cancer).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (44659)

12 ((head or neck or oral cavit* or pharyng* or hypopharyng*) adj5 tum*r).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (26377)

13 (gastrointestinal tract or mouth or pharynx or upper gastrointestinal tract).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (386258)

14 gastrointestinal tract/ or mouth/ or pharynx/ or upper gastrointestinal tract/ (107474)

15 neoplasms/ (373192)

16 14 and 15 (677)

17 13 and 15 (4869)

18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (396013)

19 diseases/ or comorbidity/ or confounding factors/ (273632)

20 diseases/ or comorbidity/ or confounding factors/ or effect modifiers/ (273632)

21 diseases/ or comorbidity/ or confounding factors/ or effect modifiers/ (273632)

22 exp Comorbidity/ (127790)

23 comorbidity.mp. (145592)

24 comorbid*.mp. (176866)

25 additional morbidit*.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (718)

26 multiple morbidit*.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (213)

27 co-existing disease.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (138)

28 comorbidit* index.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (2179)

29 comorbidity index.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (2167)

30 charlson index.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (821)

31 kaplan feinstein index.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (35)

32 greenfield index.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (7)

33 cumulative illness rating scale.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (407)

34 index of co existent disease.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (20)

35 adult comorbidity evaluation.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (93)

36 (cancer and comorbidity measure).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (6)

37 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (323692)

38 exp Socioeconomic Factors/ (414680)

39 socio economic factors.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (2531)

40 socioeconomic factors.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (94555)

41 socioeconomic.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (149702)

42 socioeconomic status.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (31915)

43 socioeconomic inequalities.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (891)

44 socioeconomic level.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (1940)

45 social class.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (53416)

46 exp Social Class/ (56749)

47 exp Poverty Areas/ or exp Poverty/ (55622)

48 poverty.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (57495)

49 social disadvantag*.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (968)

50 (soc* adj5 disadvantag*).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (5061)

51 (soc* adj5 depriv*).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (5754)

52 material deprivation.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (445)

53 material depriv*.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (448)

54 income inequalit*.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (1056)

55 health inequalit*.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (4469)

56 (health adj5 inequalit*).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (8521)

57 exp Health Status Indicators/ or exp Health Status/ or exp Health Status Disparities/ (422019)

58 deprivation index.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (431)

59 deprivation indices.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (145)

60 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 (857870)

61 exp Disease-Free Survival/ or exp Survival Analysis/ or exp Survival/ or exp Survival Rate/ (586685)

62 survival.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (1254684)

63 treatment outcome.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (978943)

64 surviv* trends.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (336)

65 (surviv* adj5 trends).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (1872)

66 exp Prognosis/ (1103497)

67 medical prognos*.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (230)

68 (recurrence adj2 surviv*).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (13252)

69 exp Hospital Mortality/ or exp Mortality/ (675205)

70 mortality.mp. (986983)

71 exp Death/ or exp Death Certificates/ or death.mp. (1075099)

72 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 (3939133)

73 exp Cohort Studies/ (1143041)

74 exp Prospective Studies/ (446709)

75 exp Retrospective Studies/mt, st [Methods, Standards] (13)

76 exp Retrospective Studies/ (584695)

77 exp Longitudinal Studies/ (739420)

78 exp Follow-Up Studies/ (908603)

79 follow up stud*.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh, tn, dm, mf] (456160)

80 73 or 74 or 75 or 76 or 77 or 78 or 79 (1971225)

81 37 or 60 (1145725)

82 18 and 72 and 80 and 81 (842)

83 remove duplicates from 82 (772)

A3.2. CINAHL Search

1. (MH"Comorbidity") OR "comorbidity" (25872)
2. "comorbidity" (892)
3. additional morbidity (108)
4. competing causes of illness (0)
5. coexisting disease (124)
6. co-existing disease (33)
7. comorbidity index (412)
8. Charlson index (313)
9. Kaplan Feinstein index (1)
10. Greenfield index (2)
11. Cumulative illness rating scale (67)
12. ACE-27 co-morbidity index (3)
13. Index of co-existent disease (5)
14. adult comorbidity evaluation (6)
15. cancer and comorbidity measure (8)
16. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 (26644)
17. "cancer" (130427)
18. "neoplasms" (169778)
19. 17 OR 18 (207691)
20. (MH"Socioeconomic Factors+") (162744)
21. "social class" (6220)
22. (MH"Social Class+") (5555)
23. "material deprivation" (98)
24. "health inequality" (159)

25. (MM"Survival") OR (MM "Survival Rate") OR (MM "Survival Analysis") (3157)
26. (MH"Survival Analysis+") (32690)
27. (MH"Prognosis+") (156570)
28. "outcomes" (229869)
29. 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 (424761)
30. 16 and 19 and 29 (840)
31. (16 and 19 and 29) AND (head and neck cancer) (36)
32. (16 and 19 and 29) AND pharyngeal cancer OR laryngeal cancer OR mouth cancer OR lip cancer OR nasopharyngeal cancer (583)

A3.3. Embase Search

1. (head and neck neoplasms).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

2. (head and neck cancer).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

3. 1 or 2

4. exp comorbidity/

5. co-morbidity.mp.

6. coexisting disease.mp.

7. 4 or 5 or 6

8. comorbidity index.mp.

9. charlson index.mp.

10. kaplan feinstein index.mp.

11. greenfield index.mp.

12. cumulative illness rating scale.mp.

13. index of coexistent disease.mp.

14. ACE-27.mp.

15. adult comorbidity evaluation.mp.

16. (cancer and comorbidity measure).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18. socioeconomic factors.mp. or exp socioeconomics/

19. exp socioeconomics/

20. socioeconomic status.mp. or exp social status/

21. socioeconomic inequalities.mp.

22. socioeconomic level.mp.

23. social class.mp. or exp social class/

24. poverty areas.mp. or exp poverty/

25. poor areas.mp.

26. poverty.mp.

27. social disadvantage.mp.

28. deprivation.mp.

29. material deprivation.mp.

30. income inequality.mp.

31. income inequalities.mp.

32. health inequality.mp. or health disparity/

33. postcode lottery.mp.

34. health status indicator.mp. or exp health survey/

35. deprivation index.mp.

36. deprivation indices.mp.

37. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38. exp cause specific survival/ or survival/ or exp survival time/ or survival.mp. or exp overall survival/ or exp cancer survival/ or exp survival rate/ or exp disease free survival/

39. (follow-up or prognos:tw).mp. or ep.fs. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

40. treatment outcome.mp. or exp treatment outcome/

41. survival trends.mp.

42. prognosis.mp. or exp prognosis/

43. prognos:.tw.

44. medical prognosis.mp.

45. exp mortality/ or mortality.mp.

46. exp death/ or death.mp. or "cause of death"/ or exp death certificate/

47. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46

48. cohort studies.mp. or exp cohort analysis/

49. prospective studies.mp. or exp prospective study/

50. retrospective studies.mp. or exp retrospective study/

51. longitudinal studies.mp. or exp longitudinal study/

52. follow-up studies.mp. or exp follow up/

53. exp epidemiology/ or epidemiological study.mp.

54. 48 or 49 or 50 or 51 or 52 or 53

55. 3 and 7 and 17 and 37 and 47 and 54

A3.4. SciELO Search

1. Head and neck neoplasms OR head and neck cancer OR pharyngeal cancer OR laryngeal cancer OR mouth cancer OR lip cancer OR nasopharyngeal cancer AND
2. Survival OR survival analysis OR survival rate OR prognosis OR outcome AND
3. Socioeconomic status OR socioeconomic deprivation OR social class OR poverty OR health inequality AND
4. Comorbidity OR co-morbidity OR coexisting illness OR co-existing illness OR competing causes of death AND
5. site:http://www.scielo.cl OR site:http://www.scielo.org.pe OR site:http://www.scielo.org.ar OR site:http://www.scielo.br OR site:http://www.scielo.org.co OR site:http://scielo.sld.cu OR site:http://scielo.isciii.es OR site:http://www.scielo.oces.mctes.pt OR site:http://www.scielo.org.ve OR site:http://www.scielo.org.mx OR site:http://www.scielo.sa.cr OR site:http://scielo.iics.una.py OR site:http://caribbean.scielo.org OR site:http://www.scielo.org.pe OR site:http://www.scielo.edu.uy OR site:http://www.scielosp.org OR site:http://socialsciences.scielo.org **(3000+ results)**

Unable to search all these terms in Google as it limits search to 32 words also returned 3000 results which was not a sensitive enough search strategy. Terms changed to

1. "Head and neck neoplasms and prognosis" site:http://www.scielo.cl OR site:http://www.scielo.org.pe OR site:http://www.scielo.org.ar OR site:http://www.scielo.br OR site:http://www.scielo.org.co OR site:http://scielo.sld.cu OR site:http://scielo.isciii.es OR site:http://www.scielo.oces.mctes.pt OR site:http://www.scielo.org.ve OR site:http://www.scielo.org.mx OR site:http://www.scielo.sa.cr OR site:http://scielo.iics.una.py OR

site:http://caribbean.scielo.org OR site:http://www.scielo.org.pe OR site:http://www.scielo.edu.uy OR site:http://www.scielosp.org OR site:http://socialsciences.scielo.org **(0 results)**

2. Head and neck neoplasms and prognosis site:http://www.scielo.cl OR site:http://www.scielo.org.pe OR site:http://www.scielo.org.ar OR site:http://www.scielo.br OR site:http://www.scielo.org.co OR site:http://scielo.sld.cu OR site:http://scielo.isciii.es OR site:http://www.scielo.oces.mctes.pt OR site:http://www.scielo.org.ve OR site:http://www.scielo.org.mx OR site:http://www.scielo.sa.cr OR site:http://scielo.iics.una.py OR site:http://caribbean.scielo.org OR site:http://www.scielo.org.pe OR site:http://www.scielo.edu.uy OR site:http://www.scielosp.org OR site:http://socialsciences.scielo.org **(162 results)**

3. Head and neck cancer prognosis site:http://www.scielo.cl OR site:http://www.scielo.org.pe OR site:http://www.scielo.org.ar OR site:http://www.scielo.br OR site:http://www.scielo.org.co OR site:http://scielo.sld.cu OR site:http://scielo.isciii.es OR site:http://www.scielo.oces.mctes.pt OR site:http://www.scielo.org.ve OR site:http://www.scielo.org.mx OR site:http://www.scielo.sa.cr OR site:http://scielo.iics.una.py OR site:http://caribbean.scielo.org OR site:http://www.scielo.org.pe OR site:http://www.scielo.edu.uy OR site:http://www.scielosp.org OR site:http://socialsciences.scielo.org **(160 results)**

A3.5. LILACS Search

1. Head and neck neoplasms
2. Oropharyngeal neoplasms
3. Pharyngeal neoplasms
4. Laryngeal neoplasms
5. Mouth neoplasms
6. Hypopharyngeal neoplasms
7. / OR 1-6 (1872 results)
8. Comorbidity
9. Co-morbidity
10. Coexisting illness
11. Competing causes of death
12. Chronic disease
13. 8 OR 9 OR 10 OR 11 (3958 results)
14. Poverty
15. socioeconomic deprivation
16. social class
17. material deprivation
18. /OR 14-17
19. 7 AND 13 AND 18 (12 results)
20. Death
21. Prognosis
22. Outcome
23. / OR 20-22 (2798 results)
24. 7 AND 13 AND 18 AND 23 (0 results)

Citation Reference list

1. Franco EL, Dibb LL, Pinto DS, Lombardo V, Contesini H. Race and gender influences on the survival of patients with mouth cancer. Journal of Clinical Epidemiology 1993; 46(1): 37-46.
2. Arbes SJ Jr, Olshan AF, Caplan DJ, Schoenbach VJ, Slade GD, Symons MJ. Factors contributing to the poorer survival of black Americans diagnosed with oral cancer (United States). Cancer Causes Control, 1999; 6: 513-23.
3. Coleman MP, Babb P, Sloggett A, Quinn M, De Stavola B: Socioeconomic inequalities in cancer survival in England and Wales. Cancer 2001, 91(1 Suppl):208-216.
4. Jones AS, Beasley N, Houghton D, Husband DJ: The effects of age on survival and other parameters in squamous cell carcinoma of the oral cavity, pharynx and larynx. Clin Otolaryngol, 1998; 23: 51–56.
5. Read WL, Tierney RM, Page NC, Costas I, Govindan R, Spitznagel EL, Piccirillo JF: Differential prognostic impact of comorbidity. J Clin Oncol 2004; 22: 3099–3103.
6. Deleyiannis FW, Thomas DB, Vaughn TL, Davis S. Alcoholism: independent predictor of survival in patients with head and neck cancer. J Natl Cancer Inst, 1996; 88:542-549.
7. Grandis JR, Snyderman CH, Johnson JT, Yu VL, D'Amico F. Postoperative wound infection: a poor prognostic sign for patients with head and neck cancer. Cancer. 1992;70:2166-2170.
8. Freng A, Daae LN, Engeland A, et al. Malignant epithelial tumours in the upper digestive tract; a dietary and socio-medical case±control and survival study. Eur J Clin Nutr 1998, 52, 271- 278.
9. de Boer MF, Van den BB, Pruyn JF, et al. Psychosocial and physical correlates of survival and recurrence in patients with head and neck carcinoma: results of a 6-year longitudinal study. Cancer 1998;83:2567e2579
10. El-Husseiny G, Kandil A, Jamshed A, et al. Squamous cell carcinoma of the oral tongue: an analysis of prognostic factors. Br J Oral Maxillofac Surg. 2000; 38: 193-199.

11. Faye-Lund H, Abdelnoor M. Prognostic factors of survival in a cohort of head and neck cancer patients in Oslo. Eur J Cancer B Oral Oncol. 1996; 32B: 83-90.
12. Chirikos TN, Reiches NA, Moeschberger ML. Economic differentials in cancer survival a multivariate analysis. J Chron Dis, 1984; 37: 183- 193.
13. Australian Institute of Health and Welfare. Cancer survival in Australia 1992-1997. Geographic categories and socioeconomic status. Canberra: AIHW; 2003.
14. Ueda K, Tsukuma H, Ajiki W, Oshima A. Socioeconomic factors and cancer incidence, mortality, and survival in a metropolitan area of Japan: a cross-sectional ecological study. Cancer Sci 2005; 96: 684 – 8.
15. Pintos J, Franco EL, Black MJ, Bergeron J, Arella M. Human papillomavirus and prognoses of patients with cancers of the upper aerodigestive tract. Cancer, 1999; 85: 1903–1909.
16. Ferrier MB, Spuesens EB, Le Cessie S, Baatenburg de Jong RJ. Comorbidity as a major risk factor for mortality and complications in head and neck surgery. Arch Otolaryngol Head Neck Surg 2005; 131: 27–32.
17. Singh B, Bhaya M, Stern J, Roland JT, Zimbler M, Rosenfeld RM, et al. Validation of the Charlson comorbidity index in patients with head and neck. cancer: a multi-institutional study. Laryngoscope 1997;107(11 Pt. 1):1469–75.
18. Coatesworth AP, Tsikoudas A, MacLennan K. The cause of death in patients with head and neck squamous cell carcinoma. J Laryngol Otol 2002; 116(4): 269–71.
19. Schrijvers CTM, Coebergh JWW, Mackenbach JP. Socioeconomic status and comorbidity among newly diagnosed cancer patients. Cancer 1997; 80:1482–1488.
20. McGuirt WF, Davis SP. Demographic Portrayal and Outcome Analysis of Head and Neck Cancer Surgery in the Elderly. Arch Otolaryngol Head Neck Surg. 1995; 121(2):150-154.
21. Magnano M, De Stefani A, Usai A, Lerda W, Albera R, Ragona R, Bussi M, Airoldi M, Cortesina G. Carcinoma of the larynx in the elderly: analysis of potentially significant prognostic variables. Aging (Milano). 1999 ;(5):316-22.
22. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008; 100: 261–269.

Methodological Quality Assessment Tool

Adapted from Marx and Marx, (221) Altman, (202) University of Montreal, (217)and Thomas *et al*. (222)

CITATION:			
ASSESSMENT QUESTIONS	**YES**	**NO**	**CAN'T TELL**
1. Were patients with the same disease included in this study?			
2. Are the individuals selected to participate in the study likely to be representative of the target population?			
3. Was a definite end point indicated?			
4. If a definite end point was not given, is there indication of a surrogate end point?			
5. Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?			
6. Is there analysis of baseline severity (e.g. TNM staging)?			
7. Are the study subjects truly representative of the population of interest?			
8. Were the study subjects chosen at a common point in the disease course?			
9. Is there indication of baseline frequency for candidate predictors (e.g. age, sex)?			
10. Does the classification of predictors make them reproducible (e.g. elderly, hypertension)?			
11. Has multivariate analysis been used to control for confounding or effect modification?			
12. Has consideration been given to Identification of the variables' importance in multivariate analysis?			
13. Have the authors accounted for the effect of treatment on predictors?			
14. Has the number of patients censored together with the reason for censoring been reported, and have these censored patients been adequately considered in the analysis?			
TOTALS			

GLOBAL RATING METHODS

LEGEND: YES (**STRONG**) CAN'T TELL (**MODERATE**) NO (**WEAK**)

GLOBAL RATING FOR THIS PAPER (circle one):

1 STRONG (All STRONG ratings with no WEAK ratings)

2 MODERATE (Mostly STRONG ratings and one WEAK rating)

3 WEAK (two or more WEAK ratings)

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (1-14) ratings?

No Yes

If yes, indicate the reason for the discrepancy

1 Oversight

2 Differences in interpretation of criteria

3 Differences in interpretation of study

Final decision of both reviewers (circle one):

1 STRONG

2 MODERATE

3 WEAK

Modified Methodological Quality Assessment Tool for Survival Studies

Adapted from Laupacis *et al*, (203) Altman, (202)Hayden *et al* (223)

CITATION:					
ASSESSMENT QUESTIONS	**YES**	**PARTLY**	**CAN'T TELL**	**NO**	**TOTAL**
1. Was there a representative and well defined sample of patients?					
2. Were these patients at a similar time point in the course of the disease?					
3. Was follow up sufficiently long and complete?					
4. Is the prognostic factor of interest adequately measured in order to limit potential bias?					
5. Were objective and unbiased outcome criteria used?					
6. Was there adjustment for important prognostic factors?					
7. Is the statistical analysis appropriate for the design of the study?					
8. Have the authors accounted for effect of treatment on predictors?					
Total					

GLOBAL RATING METHODS

LEGEND: YES (**3**) PARTLY (2) CAN'T TELL (**1**) NO (**0**)

GLOBAL RATING FOR THIS PAPER (circle one):

1 STRONG (score of 18-24)

2 MODERATE (score of 12-17)

3 WEAK (score 11 or less)

GUIDE TO ASSESSMENT QUESTIONS

1. Was there a representative and well defined sample of patients? This asks how well defined the individuals in the study are and whether they are representative of the underlying population on key characteristics, hence limiting potential bias to the study results.
2. Were these patients at a similar time point in the course of the disease? - This describes whether all patients were at a similar well defined point in the course of their disease. This calls for a clear description of the stage of disease at which patients joined the study, e.g. as duration of disease is associated with outcome, the authors should describe the duration of the illness for the sample patients. Ideally all patients should be at a similar stage such as newly diagnosed head and neck cancer (HNC). An example could be that of an HNC survival study where survival was reported at two different points in time, a) referral to oncologist and, b) the point at which HNC symptoms became apparent. The former is the more certain time point but suffers from the disadvantage that patients seek medical attention at different points of the disease course. The latter provides a more uniform starting point but is potentially imprecise because some HNCs develop insidiously and time of onset is identified retrospectively. Survival after presentation to primary healthcare services is more pertinent.
3. Was follow up sufficiently long and complete? – Follow up is important because the greater the number of patients unavailable for follow up the less accurate the estimate regarding the risk of adverse outcome. Study attrition should be minimal to limit potential bias from outcome measurement. In particular censoring asks that

consideration is made of the relation between the proportion of patients who are unavailable and those that have suffered the adverse outcome of interest. The larger the number of patients whose fate is unknown relative to the number who have suffered the event, the greater the threat to validity of the study. If reasons for unavailability or loss to follow up are omitted, the strength of inference from the study results is weaker.

4. Is the prognostic factor of interest adequately measured in order to limit potential bias? – A clear definition and description of the prognostic factor should be given. This may include information such as dose, level, duration of exposure, and clear specification of methods of measurement. Misclassification bias should be minimised by ensuring the prognostic factor measure and method are valid and reliable. An adequate proportion of the study sample should have complete data on the prognostic factor under study. The method and setting for measurement should be the same for all study participants and if data on the prognostic factor is missing, appropriate imputations should be used.
5. Were objective and unbiased outcome criteria used? – Clear description of adverse outcomes should be given at the start of the study. These vary from those that are objective and easy to measure (e.g. death) or those that need considerable judgement and are difficult to measure (e.g. quality of life or disability). To minimise bias, blinding to prognostic factor status is needed but this is not always possible.
6. Was there adjustment for important prognostic factors? – When comparing the prognosis of two groups of patients, investigators should consider whether similarities in clinical characteristics are evident and adjust analysis for any differences found. Many prognostic studies split cohorts into distinct prognostic factor groups and comparison

of the pattern and frequencies of outcomes between these groups can determine the relative risk associated with the specific prognostic factor.

7. Is the statistical analysis appropriate for the design of the study in limiting potential for presentation of invalid results? – There must be sufficient presentation of data to allow adequate review of the analysis methods used. Evidence must be available that demonstrates that the strategy for model building is appropriate (i.e. inclusion of variables) and that it is based on a conceptual model or framework. There should not be any selective reporting of results, while the selected model clearly demonstrates adequacy based on the study design.
8. Have the authors accounted for effect of treatment on predictors? – Since treatments can alter patient outcomes, these should be taken into account when analysing prognostic factors. Investigators should adjust for treatment differences in the analysis despite the acknowledgement that treatment is not a prognostic factor.

REJECTED STUDIES

This table details the reasons for rejection of the potential studies that had full text retrieval before exclusion with corresponding reasons. Studies were included in this review and meta-analysis if they addressed comorbidity and socioeconomic status (deprivation) as prognostic factors for survival outcomes measurements.

DOES NOT FOCUS ON SURVIVAL

1. De Boer MF, Van den Borne B, Pruyn JF, Ryckman RM, Volovics L, Knegt PP, Meeuwis CA, Mesters I, Verwoerd CD. Psychosocial and physical correlates of survival and recurrence in patients with head and neck carcinoma: results of a 6-year longitudinal study. Cancer, 1998; 83(12):2567-2579. (313)
2. Goeman JJ, Le Cessie S, de Jong RJB, van de Geer SA. Predicting survival using disease history: a model combining relative survival and frailty. Statistica Neerlandica. 2004; 58(1):21-34. (251)
3. Menvielle G, Luce D, Goldberg P, Leclerc A. Smoking, alcohol drinking, occupational exposures and social inequalities in hypopharyngeal and laryngeal cancer. International Journal of Epidemiology. 2004 Aug;33(4):799-806. (246)
4. Patel RS, McCluskey SA, Goldstein DP, Minkovich L, Irish JC, Brown DH, et al. Clinicopathologic and therapeutic risk factors for perioperative complications and prolonged hospital stay in free flap reconstruction of the head and neck. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck. 2010 Oct;32(10):1345-53.(248)
5. Vartanian JG, Carvalho AL, Toyota J, Giacometti Kowalski IS, Kowalski LP. Socioeconomic effects of and risk factors for disability in long-term survivors of head and neck cancer. Archives of Otolaryngology - Head and Neck Surgery, 2006 ; 132(1):32-5. (574)
6. Paleri V, Wight RG. A cross-comparison of retrospective notes extraction and combined notes extraction and patient interview in the completion of a comorbidity index (ACE-27) in a cohort of United Kingdom patients with head and neck cancer. J Laryngol Otol. [Comparative Study
7. Research Support, Non-U.S. Gov't]. 2002; 116(11):937-41.(299)
8. Singh B, Bhaya M, Stern J, Roland JT, Zimbler M, Rosenfeld RM, et al. Validation of the Charlson comorbidity index in patients with head and neck cancer: a multi-institutional study. Laryngoscope, 1997; 107(11 Pt 1): 1469-75.(163)
9. Piccirillo JF, Costas I. The impact of comorbidity on outcomes. ORL J Otorhinolaryngol Relat Spec. 2004; 66(4): 180-5.(148)
10. Zabrodsky M, Calabrese L, Tosoni A, Ansarin M, Giugliano G, Bruschini R, et al. Major surgery in elderly head and neck cancer patients: immediate and long-term surgical results and complication rates. Surg Oncol, 2004; 13(4): 249-55.(287)
11. Moore CE, Durden F. Head and neck cancer screening in homeless communities: HEAL (Health Education, Assessment, and Leadership). J Natl Med Assoc, 2010; 102(9): 811-6.(284)

12. Sethi RA, Stamell EF, Price L, DeLacure M, Sanfilippo N. Head and neck radiotherapy compliance in an underserved patient population. Laryngoscope, 2010; 120(7): 1336-41.(235)
13. Woolley E, Magennis P, Shokar P, Lowe D, Edwards D, Rogers SN. The correlation between indices of deprivation and health-related quality of life in patients with oral and oropharyngeal squamous cell carcinoma. Br J Oral Maxillofac Surg. [Comparative Study]. 2006 Jun;44(3):177-86.(122)
14. Borggreven PA, Kuik DJ, Quak JJ, de Bree R, Snow GB, Leemans CR. Comorbid condition as a prognostic factor for complications in major surgery of the oral cavity and oropharynx with microvascular soft tissue reconstruction. Head & Neck, 2003; 25(10): 808-15.(15)
15. Peters TTA, van der Laan B, Plaat BEC, Wedman J, Langendijk JA, Halmos GB. The impact of comorbidity on treatment-related side effects in older patients with laryngeal cancer. Oral Oncology. 2011 Jan;47(1):56-61.(18)
16. Paleri V, Wight RG. Applicability of the adult comorbidity evaluation - 27 and the Charlson indexes to assess comorbidity by notes extraction in a cohort of United Kingdom patients with head and neck cancer: a retrospective study. J Laryngol Otol. [Validation Studies]. 2002 Mar;116(3):200-5.(575)
17. Nobles J, Wold C, Fazekas-May M, Gilbert J, Friedlander PL. Prevalence and epidemiology of hepatitis C virus in patients with squamous cell carcinoma of the head and neck. Laryngoscope. 2004; 114(12): 2119-22.(247)
18. Nagele P, Rao LK, Penta M, Kallogjeri D, Spitznagel EL, Cavallone LF, et al. Postoperative myocardial injury after major head and neck cancer surgery. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck. 2011; 33(8): 1085-91.(286)
19. Tong H, Isenring E, Yates P. The prevalence of nutrition impact symptoms and their relationship to quality of life and clinical outcomes in medical oncology patients. Supportive Care in Cancer. 2009;17(1):83-90.(296)
20. Pytynia KB, Grant JR, Etzel CJ, Roberts D, Wei QY, Sturgis EM. Matched analysis of survival in patients with squamous cell carcinoma of the head and neck diagnosed before and after 40 years of age. Archives of Otolaryngology-Head & Neck Surgery. 2004;130(7):869-73.(288)
21. Rogers SN, Aziz A, Lowe D, Husband DJ. Feasibility study of the retrospective use of the Adult Comorbidity Evaluation index (ACE-27) in patients with cancer of the head and neck who had radiotherapy. Br J Oral Maxillofac Surg. 2006;44(4):283-8.(576)
22. Zeber JE, Copeland LA, Hosek BJ, Karnad AB, Lawrence VA, Sanchez-Reilly SE. Cancer rates, medical comorbidities, and treatment modalities in the oldest patients. Crit Rev Oncol Hematol. 2008;67(3):237-42.(259)
23. Ferrier MB, Spuesens EB, Le Cessie S, De Jong RJB. Comorbidity as a major risk factor for mortality and complications in head and neck surgery. Archives of Otolaryngology-Head & Neck Surgery. 2005;131(1):27-32.(258)
24. Grandis JR, Snyderman CH, Johnson JT, Yu VL, D'Amico F. Postoperative wound infection. Cancer. 1992;70:2166-70.(257)
25. Major SM, Bumpous JM, Flynn MB, Schill K. Quality of life after treatment for advanced laryngeal and hypopharyngeal cancer. The Laryngoscope. 2001;111:1379-82.(295)
26. Piccirillo JF, Spitznagel Jr EL, Vermani N, Costas I, Schnitzler M. Comparison of

comorbidity indices for patients with head and neck cancer. Med Care. 2004 May;42(5):482-6.(301)
27. Antunes JLF, Borrell C, Perez G, Boing AF, Wunsch V. Inequalities in mortality of men by oral and pharyngeal cancer in Barcelona, Spain and Sao Paulo, Brazil, 1995-2003. International Journal for Equity in Health. 2008; 7.(271)
28. Gourin CG, McAfee WJ, Neyman KM, Howington JW, Podolsky RH, Terris DJ. Effect of comorbidity on quality of life and treatment selection in patients with squamous cell carcinoma of the head and neck. Laryngoscope. [Comparative Study]. 2005; 115(8):1371-5.(226)
UNABLE TO OBTAIN FULL PAPER
29. Cinamon U, Hier MP, Black MJ. Age as a prognostic factor for head and neck squamous cell carcinoma: should older patients be treated differently? J Otolaryngol. 2006; 35(1):8-12.(272)
NOT ENOUGH DATA AVAILABLE
30. Cederblad L, Johansson S, Enblad G, Engstrom M, Blomquist E. Cancer of the parotid gland; long-term follow-up. A single centre experience on recurrence and survival. Acta Oncol. 2009; 48(4):549-55.(293)
31. de Cassia Braga Ribeiro K, Kowalski LP, Latorre MdRDdO. Perioperative complications, comorbidities, and survival in oral or oropharyngeal cancer. Archives of Otolaryngology -- Head & Neck Surgery. 2003; 129(2):219-28.(253)
IRRELEVANT, FAILED TO USE COMORBIDITY OR DEPRIVATION
32. van der Schroeff MP, van de Schans SAM, Piccirillo JF, Langeveld TPM, de Jong RJB, Janssen-Heijnen MLG. Conditional relative survival in head and neck squamous cell carcinoma: permanent excess mortality risk for long-term survivors. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck. 2010; 32(12):1613-8.(270)
33. El-Deiry MW, Futran ND, McDowell JA, Weymuller EA, Jr., Yueh B. Influences and predictors of long-term quality of life in head and neck cancer survivors. Archives of Otolaryngology -- Head & Neck Surgery. 2009;135(4):380-4.(268)
34. Baatenburg de Jong RJ, Hermans J, Molenaar J, Briaire JJ, le Cessie S. Prediction of survival in patients with head and neck cancer. Head & Neck. 2001; 23(9):718-24.(267)
35. Avery CM, Crank ST, Neal CP, Hayter JP, Elton C. The use of the pectoralis major flap for advanced and recurrent head and neck malignancy in the medically compromised patient. Oral Oncology. 2010; 46(11):829-33.(266)
36. de Melo GM, Ribeiro KDB, Kowalski LP, Deheinzelin D. Risk factors for postoperative complications in oral cancer and their prognostic implications. Archives of Otolaryngology-Head & Neck Surgery. 2001 ; 127(7):828-33.(265)
37. Lee MK, Nalliah RP, Kim MK, Elangovan S, Allareddy V, Kumar-Gajendrareddy P. Prevalence and impact of complications on outcomes in patients hospitalized for oral and oropharyngeal cancer treatment. Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontology. 2011; 112 (5): 581-91.(264)
38. Hansen RP, Olesen F, Sorensen HT, Sokolowski I, Sondergaard J. Socioeconomic patient characteristics predict delay in cancer diagnosis: a Danish cohort study. Bmc Health Services Research. 2008;8:49-58.(289)
39. Kruse AL, Bredell M, Luebbers HT, Grätz KW. Head and neck cancer in the elderly: a retrospective study over 10 years (1999 - 2008). Head Neck Oncol. 2010; 25-31.(262)
40. Su C-C, Chung J-A, Hsu Y-Y, Huang S-J, Lian I-B. Age at diagnosis and prognosis of oral

cancer in relation to the patient's residential area: experience from a medical center in Taiwan. Oral Oncology. [Research Support, Non-U.S. Gov't]. 2008; 44(11):1032-8.(263)

41. Jones AS, Beaseley N, Houghton D, Husband DJ. The effects of age on survival and other parameters in squamous cell carcinoma of the oral cavity, pharynx and larynx. Clin Otolaryngol. 1998; 23: 51-6.(577)
42. Coatesworth AP, Tsikoudas A, MacLennan K. The cause of death in patients with head and neck squamous cell carcinoma. J Laryngol Otol. 2002;116:269-71.(260)
43. Archer J, Hutchison I, Korszun A. Mood and malignancy: head and neck cancer and depression. J Oral Pathol Med. [Review]. 2008 ;37(5):255-70.(307)
44. Argiris A, Brockstein BE, Haraf DJ, Stenson KM, Mittal BB, Kies MS, et al. Competing causes of death and second primary tumors in patients with locoregionally advanced head and neck cancer treated with chemoradiotherapy. Clin Cancer Res, 2004; 10(6): 1956-62.(298)
45. Rosenberg PS, Socie G, Alter BP, Gluckman E. Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants. Blood. 2005 01 ;105(1):67-73.(308)
46. Nouraei SAR, Al-Yaghchi C, Sandhu GS, Giussani DA, Doyle P, Clarke PM. Incidence and significance of myocardial injury after surgical treatment of head and neck cancer. Laryngoscope. 2007; 117(9):1581-7.(283)
47. Rogers SN, Brown JS, Woolgar JA, Lowe D, Magennis P, Shaw RJ, et al. Survival following primary surgery for oral cancer. Oral Oncology, 2009; 45(3):201-11.(256)
48. Zigon G, Berrino F, Gatta G, Sanchez MJ, van Dijk B, Van Eycken E, et al. Prognoses for head and neck cancers in Europe diagnosed in 1995-1999: a population-based study. Ann Oncol. 2011;22(1):165-74.(255)
49. Sarini J, Fournier C, Lefebvre JL, Bonafos G, Van JT, Coche-Dequeant B. Head and neck squamous cell carcinoma in elderly patients - A long-term retrospective review of 273 cases. Archives of Otolaryngology-Head & Neck Surgery. 2001; 127(9):1089-92.(164)
50. Francis DO, Yueh B, Weymuller EA, Merati AL. Impact of Surveillance on Survival After Laryngeal Cancer in the Medicare Population. Laryngoscope. 2009 ;119(12):2337-44.(297)
51. Ahmad H, Jabar NA, Rahman NA, Rahman RA, Sha PP, Ramli R. Oral cavity squamous cell carcinomas in young patients in a selected Malaysian centre. Asia-Pacific Journal of Clinical Oncology. 2009 ;5(1):39-45.(254)
52. Hall SF, Groome PA, Rothwell D. The impact of comorbidity on the survival of patients with squamous cell carcinoma of the head and neck. Head & Neck, 2000;22(4):317-22.(294)
53. Wutzl A, Ploder O, Kermer C, Millesi W, Ewers R, Klug C. Mortality and causes of death after multimodality treatment for advanced oral and oropharyngeal cancer. J Oral Maxillofac Surg, 2007; 65(2):255-60.(250)
54. Kantola S, Parikka M, Jokinen K, Hyrynkangs K, Soini Y, Alho OP, et al. Prognostic factors in tongue cancer - relative importance of demographic, clinical and histopathological factors. Br J Cancer. 2000; 83(5):614-9.(269)
55. Antunes JL, Biazevic MG, de Araujo ME, Tomita NE, Chinellato LE, Narvai PC. Trends and spatial distribution of oral cancer mortality in Sao Paulo, Brazil, 1980-1998. Oral Oncology. 2001; 37(4):345-50.(252)

RESTRICTED TO RACE ONLY

56. Franco EL, Dib LL, Pinto DS, Lombardo V, Contesini H. Race and gender influences on the survival of patients with mouth cancer. J Clin Epidemiol. 1993; 46(1):37-46.(578)
57. Shiboski CH, Schmidt BL, Jordan RCK. Racial disparity in stage at diagnosis and survival among adults with oral cancer in the US. Community Dent Oral Epidemiol. 2007;35:233-40.(232)
58. Murdock JM, Gluckman JL. African-American and white head and neck carcinoma patients in a university medical center setting. Are treatments provided and are outcomes similar or disparate? Cancer. 2001; 91(1 Suppl):279-83.(229)
59. Al-Othman MOF, Morris CG, Logan HL, Hinerman RW, Amdur RJ, Mendenhall WM. Impact of race on outcome after definitive radiotherapy for squamous cell carcinoma of the head and neck. Cancer, 2003; 98(11):2467-72.(224)
60. Moore SP, Green AC, Garvey G, Coory MD, Valery PC. A study of head and neck cancer treatment and survival among indigenous and non-indigenous people in Queensland, Australia, 1998 to 2004. BMC Cancer. 2011; 11: 460-466.(227)
61. Ragin CC, Langevin SM, Marzouk M, Grandis J, Taioli E. Determinants of head and neck cancer survival by race. Head and Neck. 2011;33(8):1092-8.(230)
62. Moore RJ, Doherty DA, Do KA, Chamberlain RM, Khuri FR. Racial disparity in survival of patients with squamous cell carcinoma of the oral cavity and pharynx. Ethn Health, 2001; 6(3-4): 165-77.(228)
63. Schrank TP, Han Y, Weiss H, Resto VA. Case-matching analysis of head and neck squamous cell carcinoma in racial and ethnic minorities in the United States--possible role for human papillomavirus in survival disparities. Head & Neck. [Comparative Study]. 2011 Jan;33(1):45-53.(231)
64. Tomar SL, Loree M, Logan H. Racial differences in oral and pharyngeal cancer treatment and survival in Florida. Cancer Causes Control. 2004 Aug;15(6):601-9.(233)
NOT A PRIMARY STUDY
65. Babin E, Sigston E, Hitier M, Dehesdin D, Marie JP, Choussy O. Quality of life in head and neck cancers patients: Predictive factors, functional and psychosocial outcome. European Archives of Oto-Rhino-Laryngology. [Review]. 2008 Mar;265(3):265-70.(302)
66. Casasola RJ. Head and neck cancer. J R Coll Physicians Edinb. [Review]. 2010 Dec;40(4):343-5(306)
67. Nutting CM, Robinson M, Birchall M. Survival from laryngeal cancer in England and Wales up to 2001. Br J Cancer. [Comment]. 2008 Sep 23;99 Suppl 1:S38-9.(305)
68. Allison P, Locker D, Feine JS. The role of diagnostic delays in the prognosis of oral cancer: a review of the literature. Oral Oncology. [Review]. 1998 May;34(3):161-70.(303)
69. Piccirillo JF. Impact of comorbidity and symptoms on the prognosis of patients with oral carcinoma. Archives of Otolaryngology -- Head & Neck Surgery, 2000 Sep;126(9):1086-8.(139)
REPORTED IN A DIFFERENT PAPER
70. Jameson MJ, Karnell LH, Christensen AJ, Funk GF. First-year trends in self-reported general health predict survival in patients with head and neck cancer. Archives of Otolaryngology-Head & Neck Surgery, 2008; 134(9): 958-64.(292)
71. Alho OP, Hannula K, Luokkala A, Teppo H, Koivunen P, Kantola S. Differential prognostic impact of comorbidity in head and neck cancer. Head and Neck-Journal for the Sciences and Specialties of the Head and Neck. 2007 Oct;29(10):913-8.(156)
USED A DIFFERENT HNC DEFINITION

72. Anonymous. Octogenarians face poor outcomes from cancer surgery. AORN Journal. 2008;87(3): 516.(94)
73. Sloggett A, Young H, Grundy E. The association of cancer survival with four socioeconomic indicators: a longitudinal study of the older population of England and Wales 1981-2000. BMC Cancer. 2007; 7(1):20. (282)
74. Ueda K, Tsukuma H, Ajiki W, Oshima A. Socioeconomic factors and cancer incidence, mortality, and survival in a metropolitan area of Japan: A cross-sectional ecological study. Cancer Science. 2005;96(10):684-8. (281)
75. Schrijvers CT, Coebergh JWW, Mackenbach JP. Socioeconomic status and comorbidity among newly diagnosed cancer patients. Cancer. 1997;80:1482-8.(186)
76. Jeffreys M, Sarfati D, Stevanovic V, Tobias M, Lewis C, Pearce N, et al. Socioeconomic inequalities in cancer survival in New Zealand: The role of extent of disease at diagnosis. Cancer Epidemiology Biomarkers and Prevention. 2009 March;18(3):915-21.(279)
77. Brown KW, Levy AR, Roseberger Z, Edgar L. Psychological distress and cancer survival: a follow-up 10years after diagnosis. Pychosomatic Medicine. 2003;65:636-43.(515)
78. Manton KG, Wrigley JM, Cohen HJ, Woodbury MA. Cancer mortality, aging, and patterns of comorbidity in the United States: 1968 to 1986. Journal of Gerontology. 1991;46(4):S225-34.(277)
79. Menvielle G, Kunst AE, Stirbu I, Borrell C, Bopp M, Regidor E, et al. Socioeconomic inequalities in alcohol related cancer mortality among men: To what extent do they differ between Western European populations? Int J Cancer. 2007 Aug;121(3):649-55.(244)

HPV RELATED PAPERS

80. Pintos J, Franco EL, Black MJ, Bergeron J, Arella M. Human papillomavirus and prognoses of patients with cancers of the upper aerodigestive tract. Cancer. 1999;85:1903-9.(237)
81. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008; 100: 261-9.(69)
82. Weinberger PM, Merkley MA, Khichi SS, Lee JR, Psyrri A, Jackson LL, et al. Human papillomavirus-active head and neck cancer and ethnic health disparities. Laryngoscope, 2010; 120(8): 1531-7.(63)
83. Settle K, Posner MR, Schumaker LM, Tan M, Suntharalingam M, Goloubeva O, et al. Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients. Cancer Prev Res 2009 Sep;2(9):776-81.(238)
84. Bleyer A. Cancer of the oral cavity and pharynx in young females: increasing incidence, role of human papilloma virus, and lack of survival improvement. Seminars in Oncology. 2009 October;36(5):451-9.(236)
85. Lill C, Kornek G, Bachtiary B, Selzer E, Schopper C, Mittlboeck M, et al. Survival of patients with HPV-positive oropharyngeal cancer after radiochemotherapy is significantly enhanced. Wiener Klinische Wochenschrift, 2011; 123(7-8):215-21.(60)

CASE CONTROL STUDIES

86. Johnson S, McDonald JT, Corsten M, Rourke R. Socio-economic status and head and neck cancer incidence in Canada: A case-control study. Oral Oncology. 2010 March;46(3):200-3.(242)

87. Freng A, Daae LNW, Engeland A, Norum KR, Sander J, Solvoll K, et al. Malignant epithelial tumours in the upper aerodigestive tract: a dietary and socio-medical case-control and suvival study. European Journal of Clinical Nutrition. 1998; 52: 271-8.(240)
88. Bossetti C, Franceschi S, Negri E, Talamini R, Tomei F, La Vecchia C. Changing socioeconomic correlates for cancers of the upper digestive tract. Ann Oncol. 2001;12:327-30.(579)
89. Groome PA, Schulze KM, KM, Keller S, Mackillop WJ. Demographic differences between cancer survivors and those who die quickly of their disease. Clinical Oncology. 2008 October;20(8):647-56.(241)
90. Nichols AC, Bhattacharyya N. Racial differences in stage and survival in head and neck squamous cell carcinoma. Laryngoscope. 2007 May;117(5):770-5.(243)
91. Moles DR, Fedele S, Speight PM, Porter SR, Silva ID. Oral and pharyngeal cancer in South Asians and non-South Asians in relation to socioeconomic deprivation in South East England. Br J Cancer. 2008 Feb;98(3):633-5.(245)

Data Abstraction Tables

COMORBIDITYAND/SOCIOECONOMIC STATUS (SES) STUDIES

CITATION (FIRST AUTHOR, COUNTRY, YEAR,)	NUMBER (N)	TUMOUR SITE	PROGNOSTIC FACTOR AND MEASUREMENT METHOD	RECRUITMENT PERIOD	SURVIVAL ANALYSIS REPORTED/ ENDPOINTS CONSIDERED	ADJUSTMENT FOR CONFOUNDING	QUALITY RATING
Allareddy(341) USA 2006	24 803	Head and neck cancer	**Comorbidity**- No tool but comorbid disorders listed **SES**- Insurance status	2000- 2003	Multivariate OR for death **Comorbidity** Pulmonary circulation disorders OR=1.90 (CI 0.99,3.64) Congestive heart failure OR= 2.17 (CI 1.79,2.63) p<.0001 Neurological disorders OR=1.71 (CI 1.38,2.12) p<.0001 Renal failure OR=1.49 (CI 1.02, 2.17) p0.03 Liver disease OR=1.37 (CI 1.01,1.86) p0.03 Coagulopathy OR=1.54 (CI 1.11,2.15) p.009 Weight loss OR=1.16 (CI 0.98,1.38) p0.08 Fluid & electrolyte disorders OR=1.73 (CI 1.51,1.98) p<.0001 Deficiency aneamias OR=1.13 (CI 0.95,1.36) p<.0001 **Insurance** Self pay/no charge/others OR=1.42 (CI 1.10,1.83) p.006 Private Reference category	Controlled for comorbid conditions, insurance status, complications of medical or surgical care hospital bed size, hospital location and hospital teaching status	10/24 Weak

Andersen(365) Denmark 2008	4857	Mouth, pharynx and larynx cancer	**SES and Comorbidity**- Social class and Charlson comorbidity index	1994- 2003	5yr RS Men vs. Women Social class Mouth and pharynx Creative core 39% (CI 28,35) vs. 49% (CI 37-64) Creative professional 43% (CI 37-,50) vs. 46% (CI34-62) Bohemian 27% (CI 13-55) vs. 0 Service 32% (CI 28-36) vs. 45% (CI 40-50) Manual 32% (CI 29-35) vs. 43% (CI 32-57) Agricultural 38% (CI 25-56) vs. 0 Unknown 26% (CI 20-34) vs. 35% (CI 29-43) CCI 0 35% (CI 33-38)vs. 46% (CI 42-51) CCI 1 27% (CI 22-32) vs. 36% (CI 28-46) CCI ≥2 27% (CI 20-35) vs. 29% (CI 19-43) Larynx Social class Creative core 83% (CI 70,97) vs. 59% (CI 59-59) Creative professional 63% (CI 56,72) vs. 82% (CI 59-114) Bohemian 19% (CI 7,48) vs. 0 Service 53% (CI 41-60) vs. 55% (CI 47-64) Manual 52% (CI 48-56) vs. 49% (CI 34-69) Agricultural 55% (CI 41-73)vs. 101% Unknown 49% (CI 40,61)vs. 53% (CI43-66) CCI 0 56% CI 53-60) vs. 58% (52-66) CCI 1 56% (CI 49-63)vs. 44% (CI 32-61) CCI ≥2 38% (30-50) vs. 61% (CI 44-85)	Not described	16/24 Moderate
Gourin(340) USA 2006	1128	Head and neck cancer	**Comorbidity**- Modified Medical Comorbidity Index SES- Payer status (i.e. insurance, aid or none)	January 1985- March 2002	5yr DSS- Comorbidity 0/1 All 43.8%, Black 30.3%, White 53.8% p<.0001 2/3 All 34.5%, Black 17.8%, White 47.5% p<.0001 5 yr DSS- Payer status Insurance- All 45.8%, Black 43.5%, White 46.9% p .5026 Aid- All 43.9%, Black 28.0%, White 60.1% p<.0001 None- All 41.6%, Black 29.5%, White 52.8% p.0004	Stepwise variable selection adjusting for patient, tumour and treatment characteristics	24/24 Strong

COMORBIDITY STUDIES

CITATION (FIRST AUTHOR, COUNTRY, YEAR,)	NUMBER (N)	TUMOUR SITE	PROGNOSTIC FACTOR AND MEASUREMENT METHOD	RECRUITMENT PERIOD	SURVIVAL ANALYSIS REPORTED/ ENDPOINTS CONSIDERED	ADJUSTMENT FOR CONFOUNDING	QUALITY RATING
Hathaway(428) USA 2001	330	Metastatic squamous cell carcinoma of the head and neck	**Comorbidity**-Modified medical comorbidity index	Not given	DSS comorbidity adjusted risk ratio None 1 (reference) Mild 0.9 (CI 0.6-1.4) Moderate 1.4 (CI 0.9-2.1) Severe 1.1 (CI 0.6-2.1) **Comorbidity severity did not affect disease specific survival**	Adjusted for simultaneous impact treatment	11/24 Weak
Powles(580) UK 2004	7	Head and neck cancer	**Comorbidity**-HIV	1986- 2001	Median OS 28 months	Not described	10/24 Weak
Paleri(494) England 2003	180	Laryngeal squamous cancer	**Comorbidity**-ACE-27 index	1 January 1993- 31 December 1997	Mortality rate Cardiovascular 27.4% Respiratory 32.1% Gastrointestinal 41.1% Endocrine 40% Neurological 70% Malignancy 46.6% Nil comorbidity 11.1%	Not specified	10/24 Weak
Liu(352) China 2006	37	Nasopharyngeal cancer	**Comorbidity**-Diabetes mellitus	Not specified	4yr DFS Diabetics vs. Non-diabetics 35.1% vs. 65.1% (Wilcox on p=.005)	Not described	15/24 Moderate
Leitner(345) UK 2001	286	Oral cavity and oropharyngeal squamous cell carcinoma	**Comorbidity**-Previous medical history	1992- 1997	OS for patients with comorbidity (previous medical history) 1year 87 (3%) 3 year 69 (5%)	Not described	13/24 Moderate

					5 year 56 (6%)		
Kutler(581) USA 2003	19	Head and neck squamous cell carcinoma	**Comorbidity**-Fanconi's anaemia	1982- 2001	OS 26% 2yr DSS 49% 2yr OS 49% 2 yr RFS 42%	Not described	17/24 Moderate
Ramakrishnan(162) UK 2007	59	Nasopharyngeal cancer	**Comorbidity**-ACE-27 index	1989-2003	5yr DSS 41.2% Comorbidity present vs. Absent HR= 1.81 (CI 0.92,3.57) p=0.083	Adjusted for stage and age	Moderate 16/24
De Cassia Braga Ribiero(140) Brazil 2000	110	Oral carcinoma	**Comorbidity**-National cancer Institute (NCI) comorbidity score and Charlson Comorbidity Index (CCI)	1 January 1990- 31 December 1994	5yr OS NCI Level 1 41.5% Level 2 22.2% p=0.04 CCI Grade 0 30.8% Grade 1 36.2% Grade 2 33.3% p=0.72	Adjusted for daily alcohol consumption, neck lump, dysphagia, hematocrit of 0.35 or lower, age over 50, NCI level 2, earache, and oral cavity bleeding	Moderate 15/24
Woodard(351) USA 2007	143	Laryngeal cancer	**Comorbidity**-No measurement tool described	28 July 1994- 11 August 2005	Median survival Comorbidity ≤2 51 months >2 16 months p=0.02 Cardiovascular comorbidity Yes 22 months No 35 months P=0.04	Controlled for cancer site, T stage, N stage, number of comorbidities, and cardiovascular comorbidity	16/24 Moderate
Hall(138) Canada 2002	379	Head and neck cancer	**Comorbidity**-CIRS, KFI, CCI, IECD, Chronic disease scale (CDS)	1990-1996	Risk of death RR estimate CIRS Level 1(0-2) 1.0 Level 2 (3-8) 1.66 (1.06-2.56) Level 3(>8) 2.18 (1.31-3.63)	Controlled for age, sex, site and stage	20/24 Strong

					KFI Level 1 (0,1) 1.00 Level 2 (2) 1.38 (0.99-1.93) Level 3 (3) 3.03 (2.12-4.33) CCI Level 1(0,1) 1.00 Level 2 (2) 1.70 (1.20-2.42) Level 3 (>2) 2.82 (1.77-4.48) IECD Level 1 (1) 1.00 Level 2 (2&3) 1.37 (0.96-1.95) Level 3 (4) 3.17 (2.13-4.72)		
Hernandez Montero(187) Spain 2008	99	Hypopharyngeal and laryngeal cancer	**Comorbidity**-WUHNCI	1997- 2002	Odds of overall survival Comorbidity OR 1.552 (1.088-2.214) p0.015 For each additional degree of comorbidity, the risk of death increases 1.552 times Odds for specific overall survival Comorbidity OR 1.446 (0.971-2.153) p 0.070 For each comorbidity stage, the original tumour death risk increases by 44.6%	Controlled for response to neoadjuvant chemotherapy, staging and comorbidity	23/24 Strong
Chen(161) USA 2001	182	Laryngeal squamous cell carcinoma	**Comorbidity**-Modified medical comorbidity index	1 January 1990- 31 December 1995	5yr Disease Specific Survival Comorbidity status OR 2.1 (1.3-3.5) p0.003 Overall Survival	Adjusted for age, gender, race, marital status, cigarette smoking, other	19/24 Strong

					Comorbidity status OR 2.3 (CI 1.4-3.6) p0.0005	tobacco use, and alcohol use	
Castro(427) Brazil 2007	90	Laryngeal squamous cell carcinoma	**Comorbidity**- Cumulative illness rating scale (CIRS), Kaplan Feinstein index (KFI), Charlson index (CCI), Index of coexistent disease (IECD), Adult comorbidity evaluation (ACE-27) index, Alcohol-tobacco-related comorbidities index (ATC) and the Washington university head and neck comorbidity index (WUHNCI)	January 1996- December 2000	4yr OS CIRS Group ≤2 67.0% vs. Group >2 50.0% (p=0.006) KFI Group 0 81.8% vs. Group 1-2 64.9% vs. Group ≤3 47.6% (p=0.001) CCI Group 0 75.9% vs. Group 1 59.8% vs. Group ≤2 52.9% (p=0.019) IECD Group 0 80.2% vs. Group ≤1 57.3% (p=0.013) ACE-27 Grade 0 88.2% vs. Grade 1 59.0% vs. Grade≤2 53.3% (p=0.010) ATC Group 0 80.8% vs. Group ≤1 56.5% (p=0.005) WUHNCI Group 0 78.2% vs. Group ≤1 55.5% (p=0.004)	Not described	Strong 20/24
Borggreven(96) The Netherlands 2004	170	Oral and oropharyngeal cancer	**Comorbidity**- ACE-27 index	1 January 1995- 31 December 1998	5yr DSS ACE-27 grade ≤ 2 63% ACE-27 grade 3 31% 5yr OS ACE-27 grade ≤ 2 64% ACE-27 grade 3 29% (p=0.039) No statistically significant relationship found in Cox	Controlled for confounding by age, gender, tumour site, tumour stage, margin status, post operative radiotherapy and stratification for complications	Strong 24/24

						also carried out	
Datema(330) The Netherlands 2009	1371	Head and neck cancer	**Comorbidity**- ACE-27 index	1981- 1998	Impact on overall survival ACE-27 Grade 0 HR= 1.00 Grade 1 HR= 1.043 (CI 0.88-1.24) Grade 2 HR= 1.379 (CI 1.15- 1.65) Grade 3 HR= 2.229 (CI 1.73-2.87)	Analysis was adjusted for primary tumour site, age at diagnosis, sex, prior malignancies, comorbidity and TNM classification	21/24 Strong
Yung(150) USA 2008	183	Squamous cell carcinoma of the oral cavity, oropharynx and larynx	**Comorbidity**- ACE-27 index	1 January 1997- 31 December 1998	Risk of death from baseline to outcome (HR) Mild 2.6 (CI 1.1-6.2) Moderate 2.8 (CI 1.2-6.8) Severe 6.7 (2.7-16.7) Risk of death for worsened scores (adjHR) None to mild 1.4 (CI 0.4-5.3) None to moderate 1.7 (CI 0.4-6.7) None to severe 3.4 (CI 1.1-10.1) Mild to moderate 2.7 (CI 0.8-8.9) Mild to severe 2.9 (CI 1.1-7.9) Moderate to severe 3.3 (CI 1.3-8.6)	Controlled for age, sex, race and stage of tumour	19/24 Strong
Tanvetyanon(333) USA 2009	103	Head and neck cancer	**Comorbidity**- Charlson comorbidity index and ACE-27 index	January 1998- 2008	2yr OS 40% (CI 29.4,50.5) Multivariable survival CCI 0 HR 1.00	Controlled for CCI, ACE-27, age, organ dysfunction, and recurrent T	24/24 Strong

					CCI ≥ 1 HR 2.29 (CI 1.34,3.91) Univariable p=0.002 Multivariable p=0.016 ACE-27 0 or 1 HR 1.00 2 or more HR 2.68 (1.51,4.78) Univariable p=0.001 Multivariable p=0.032	stage	
Soares(334) Brazil 2009	121	Head and neck cancer	**Comorbidity**- ACE-27 index	May 2000- December 2005	Univariate analysis OR risk of death Comorbidity none-mild OR 1.00 Moderate or severe OR 2.50 (CI 1.04,6.00) p=0.040	Adjusted for type of cancer, extensive disease, cancer, status, performance status, weight loss, moderate or severe comorbidity, sepsis, the need for mechanical ventilation (MV) and number of organ failures during ICU stay	22/24 Strong
Liu(337) Taiwan 2010	214	Head and neck cancer	**Comorbidity**- Charlson comorbidity index	January 2000- December 2003	3yr OS 21.9% 3yr DSS 24.4% Univariate 3yr OS CCI 0 25.9% CCI 1 21.8% CCI ≥2 3.5% P<.0001 Univariate 3yr DSS CCI 0 26.9% CCI 1 28.3% CCI ≥2 7.5%	Controlled for marital status, age, gender, smoking, betel quid chewing, education years, occupation status, tumour site, T stage, N stage,	23/24 Strong

					P<.0001 Multivariate survival OS CCI (0-1 vs. CCI ≥2) HR 2.7 (CI 1.7,4.2) DSS CCI (0-1 vs. CCI ≥2) HR 2.4 (CI 1.5,3.8) p<.001	Karnofsky performance score, AJCC stage, treatment with 2D technique, a radiotherapy alone dose <70Gy and no radiotherapy plus chemotherapy,	
Piccirillo(148) USA 2004	19 268	Head and neck cancer	**Comorbidity**-ACE-27 index	1 January 1995- 31 January 2001	OS No comorbidity HR=1.00 Mild HR=1.03 (CI 0.80,1.32) Moderate HR=1.92 (CI 1.50,2.47) Severe HR=2.48 (CI 1.77,3.47) p<.001 $X^{2/3}$ C statistic = 46.31	Used partial likelihood ratio to test independent contribution of comorbidity	20/24 Strong
Mell(339) USA 2010	479	Head and neck cancer	**Comorbidity**-Charlson comorbidity index	August 1993- November 2004	CCI competing mortality HR= 1.24 (CI 1.05,1.47) p=0.012	Adjusted for age, body mass index, female sex, and comorbidity status	21/24 Strong
Terhaard(331) The Netherlands 2008	666	Salivary gland cancer	**Comorbidity**-ACE-27 index	1985- 1994	All cause mortality Grade 0 comorbidity vs. Grade 1 comorbidity HR=1.5 (CI 1.1, 2.1) p<.007 Grade 0 comorbidity vs. Grade 2 comorbidity HR= 1.7 (CI 1.2,2.5) p=.003 Grade 0 comorbidity	Adjusted for clinical AJCC 2000 stage, pain, sex and age	22/24 Strong

					vs. Grade 3 comorbidity HR= 2.7 (CI 1.5,4.7) p=.001		
Teppo(290) Finland 2009	221	Larynx, tongue and pharynx cancer	**Comorbidity**- Charlson Comorbidity index	January 1986- December 1996	OS Low comorbidity HR=1.0 Modest HR=0.9 (CI 0.4,2.2) High HR=5.6 (CI 2.3,13.5) p<.001 DSS Low comorbidity HR=1.0 Modest HR=2.7 (CI 0.9,8.6) High HR=5.0 (CI1.3,19.2) p.019	Adjustments made for patient and professional diagnostic delays, comorbidity status, sex, age, sub site of tumour and cancer stage	21/24 Strong
Singh(163) USA 1997	88	Head and neck cancer	**Comorbidity**- Charlson comorbidity index	1 January 1983- 30 June1994	Charlson index grade (High vs. Low) RR 2.35 (CI 1.23,4.46) p=0.009	Controlled for cancer stage	18/24 Strong
Kuo(582) Taiwan 2011	27 424	Head and neck cancer	**Comorbidity**- Charlson comorbidity index	1997- 2008	Radiotherapy group (RT) HR- 1.34 p=0.0001 Only surgical treatments or combination of surgical treatments and radiation (ORT) HR= 1.22 p=0.0065 Only chemotherapy or combination of chemotherapy and radiation (CRT) HR= 1.26 p=0.0014	Adjusted for age, gender, area of living, occupation categories and disease sites	22/24 Strong
Reid(335) USA 2001	9386	Head and neck cancer	**Comorbidity**- Charlson Comorbidity index	1985- 1993	Estimated relative hazards (RH) Charlson comorbidity index Grade 0 RH=1	Regression and stratified analysis of age and date at diagnosis,	Strong 22/24

					Grade 1 RH=1.33 (CI 1.21,1.47) Grade 2 RH=1.83 (CI 1.64,2.05) p<0.00001 RH for all cause mortality Charlson comorbidity Grade 0 RH=1 Grade 1+ RH=1.50 (CI 1.43,1.68)	marital status, gender, race, anatomic site, historic stage, education treatment, histological grade, marital status, and socioeconomic status	
Sabin(276) USA 1999	152	Laryngeal cancer	**Comorbidity**-Charlson Comorbidity Index	January 1984- February 1994	5yr DSS p=0.0002 Low comorbidity 47% High comorbidity 32% Overall 44% RR High comorbidity vs. Low 1.57 (CI 1.18,2.08) p=0.002	Adjusted for comorbidity, tumour stage and age	19/24 Strong
Sanabria(155) Brazil 2007	310	Head and neck cancer	**Comorbidity**-ACE-27 index	1 January 1990- 31 December 2003	5yr DFS 63.1% 5yr OS 42.8% 5yr DSS 55.8% DFS ACE-27 Group 0 DFS 68.3% HR=1 Group 1 57.0% HR= 1.45 (CI 0.87,2.42) Group 2 75.0% HR=0.92 (0.55,1.55) Group 3 60.7% HR=1.28 (CI0.67,2.44) p=0.41 OS Group 0 56.9% HR=1 Group 1 46.0% HR=1.83 (CI 1.24,2.71) Group 2 30.2% HR=1.97 (CI 1.42,2.71) Group 3 21.6% HR=2.08 (CI 1.38,3.11)	Used a stepwise backward Univariate and multivariate analysis gender, age, clinical stage, tumour site, neck dissection, treatment type, ACE-27, and Karnofsky index	Strong 21/24

					P<.001 CSS Group 0 64.5% Group1 58.0% HR=1.52 (CI 0.95,2.42) Group 2 43.6% HR=1.71 (CI 1.15,2.56) Group 3 45.2% (CI 0.91,2.62) P=.007		
Sanabria(346) Brazil 2008	477	Head and neck cancer	**Comorbidity**-Washington University Head and Neck Comorbidity Index (WUHNCI)	1 January 1993- 31 December 2003	5yr OS 42.3% 5yr DSS 56.3% WUHNCI OS 0 reference HR=1 1 HR=1.85 (CI 1.35,2.53) 2 HR=1.33 (CI 0.95,1.85) >=3 HR=1.65 (CI 1.12,2.44)	Adjusted for age, sex and clinical stage	20/24 Strong
Deleyiannis(310) USA 1996	649	Head and neck cancer	**Comorbidity**-Alcoholism	1 September 1983- 28 February 1987	RR for death Alcoholism 2.06 (CI 1.43,2.98)p<.001 History of alcohol-related health problems RR for death 2.76 (CI 1.69,4.49) p<.0001	Adjusted for age, site of cancer, histopathologic grade, anatomical stage, and antineoplastic treatment	24/24 Strong
Ledeboer(332) The Netherlands 2011	262	Head and neck cancer	**Comorbidity**-ACE-27 index	November 2003- November 2006	ACE-27 multivariate analysis Grade 0 HR Referent Grade 1 HR 0.9 (CI 0.6, 1.3) Grade 2 HR 0.7 (CI 0.5, 1.1) Grade3 HR 1.8 (CI 1.1, 3.1)	Prognostic importance of variables on survival tested univariately followed by multivariate Cox regression.	19/24 Strong

Grignon(291) USA 2007	571	Head and neck cancer- oral cavity, oropharynx, larynx and hypopharynx	**Comorbidity**- ACE-27 index and Medical outcomes study 36 item short-term health survey (SF-36)	1 January 1995- 30 November 2004	5yr Observed survival No comorbidities 67.2% Severe comorbidities 42.0% 5yr DSS Severe comorbidities 63.2% Moderate comorbidities 74.8% 5yr Observed Survival (health measures only) ACE-27 Risk ratio 1.24 p.002 Physical component summary Risk ratio 0.97 p<.001 5yr observed survival (health measures and disease factors) ACE-27 Risk ratio 1.25 p .003 Physical component summary Risk ratio 0.97 p<.001	Adjusted for comorbidity rating, self reported health scores in multivariate analysis	20/24 Strong
Van de Schans(350) The Netherlands 2007	Not specified	Larynx cancer	**Comorbidity**- Modified Charlson Comorbidity Index	1995- 1 January 2006	HR for death Older patients with COPD vs. Older patients without Model A unadjHR 2.0 (CI 1.5,2.7) p=.05 Model B 1.8 (CI1.4,2.5) p=.05 Model C HR 2.0 (CI 1.5,2.8) p=.05 Model D HR 2.1. (CI 1.5,2.9) p=.05	Adjusted for gender, socioeconomic status, stage, treatment, and cardiovascular disease	Strong 18/24

Singh(583) USA 1998	70	Head and neck squamous cell carcinoma	**Comorbidity**- Kaplan Feinstein Index	1 January 1983- 30 June 1994	Median DFS KFI Grade0-1 21.6 months Grade 2/3 11.1 months p.045 Median survival Grade 0-1 57.6 months Grade2/3 13.7 months p.030 DFS KFI Grades High vs. Low RR 2.29 (CI 1.18, 4.41) p.01 Tumour specific survival KFI Grades High vs. Low RR 2.37 (CI 1.12,5.05) p.01	Adjusted for tumour stage and HIV infection in multivariate analyses	21/24 Strong
Gimeno-Hernandez(338) Spain 2011	231	Laryngeal cancer	**Comorbidity**- Charlson Comorbidity Index	1 January 1995-31 December 2006	Overall mortality Comorbidity Severe vs. Non severe adjHR 3.81 (CI 1.36, 10.69) p<0.011 Specific mortality Comorbidity Severe vs. Non severe adjHR 1.85 (CI 1.07, 3.17) p=0.028	Controlled for influence of tumour stage	19/24 Strong
Pedruzzi(343) USA 2008	366	Oropharyngeal squamous cell carcinoma	**Comorbidity**	1 January 1990- 31 December 2001	5yr OS Comorbidity None 26.3% 1 8.3% 2 18.9% 3 11.8% 5yr DFS None 23.4% 1 8.1% 2 15.5% 3 11.8%	Conducted univariate analysis using stepwise variable analysis factors used	18/24 Strong

Ghobadi(336) USA 2009	182	Head and neck cancer	**Comorbidity**- Charlson Comorbidity Index (CCI)	January 2000- June 2007	CCI HR 1.11 (CI 0.99, 1.24) p=0.08 Median OS 883 days	Adjustment for CCI, age, race, alcohol use, primary site, treatment and stage	22/24 Strong
Homma(160) Japan 2009	156	Carcinomas of the hypopharynx	**Comorbidity**- ACE-27	1995- 2005	OSR Comorbidity None-Mild 45.1% Moderate-Severe 27.7% p=0.0073 HR None-Mild 1.80 (CI 1.21, 2.68) p=.0036 Moderate-Severe 1	Adjusted for age, stage and comorbidity	20/24 Strong
Wu(347) Taiwan 2010	372	OSCC excluding salivary gland, tonsils, oropharynx and hypopharynx	**Comorbidity**- Diabetes status	Jan 2002- Dec 2005	HR for OS Diabetics vs. Non Diabetics 2.22 (CI 1.27, 3.88) p=.008 DFR 2.96 (CI 1.88, 4.68) p<.001 RFS HR 2.66 (CI 1.28, 5.54) p=.009	Adjustment for confounding but specific factors not identified	20/24 Strong
Peters (213) Netherlands 2011		Pharyngeal cancer	Comorbidity – ACE-27	1997-2007	OR for OS (p<0.001) None Reference category Mild 0.323 (CI 0.063-1.686 Moderate 0.748 (CI 0.133-4.187) Severe 0.435 (CI 0.041-4.614)	Adjustment for age, sex and birth cohort	21/24 Strong
Ramroth (214) 2011 Germany	594	Laryngeal cancer	**Comorbidity**- CCI	1998-2004	5yr OS 5yr DFS None 73.4% 85.4% Mild 65.8% 82.4% Moderate 59.2% 84.1% Severe 52.1%	Not described	18/24 Strong

					74.5% Crude HR 2.1 AdjHR 1.4		
Sadat (215) 2012 Germany	169	Squamous cell HNC	**Comorbidity-** Karnofsky performance score	1996-2004	OS 20% KPI 80-100%, OS 8% KPI ≤ 70% (p < 0.001). HR 0.13 (p=0.48)	Not described	16/24 Moderate
Zhang (349) 2013 China	205	Laryngeal cancer	**Comorbidity-** CCI	Jan 2003-Nov 2008	HR CCI 1-2 2.00 (1.05;3.81) p=0.036 adjHR 2.69 (1.38;5.24) p=0.004 CCI≥3 2.68 (1.35;5.31) (p=0.005) adjHR 3.6 (1.77;7.33) p<0.001	Not described	20/24 Strong
Yang (348) 2015 Taiwan	4095	Nasopharyngeal cancer	**Comorbidity-** Age adjusted CCI and HNC CCI	2007-2011	Age related CCI, Head and neck CCI and CCI Higher comorbidity equates to poor survival ROC p<0.001 5yr OS CCI 0 = 77% CCI 1-5 = 63% CCI≥6 = 40%	Not described	20/24 Strong

SOCIOECONOMIC STATUS (SES) STUDIES

CITATION (FIRST AUTHOR, COUNTRY, YEAR,)	NUMBER (N)	TUMOUR SITE	PROGNOSTIC FACTOR AND MEASUREMENT METHOD	RECRUITMENT PERIOD	SURVIVAL ANALYSIS REPORTED/ ENDPOINTS CONSIDERED	ADJUSTMENT FOR CONFOUNDING	QUALITY RATING
Paterson(353) England 2002	20 131	All head and neck cancers	**SES**- Carstairs Index	Not specified	5 yr RSR Most affluent vs. Most Deprived= 49.9% (48.8, 51.0) p<.001 (1yr) p<.01 (thereafter) Carstairs 1/ 2 vs. 3-5 Age 40-59 59.5% (CI 55.4, 63.8) vs. 52.4% (CI 50.1,54.9) p=.001 Age 60-79 51.1% 9 (CI 48.4,53.9) vs. 46.2% (CI 44.7,47.8) p=.001	Corrected for social class differences in mortality in general population. Used life table method to assess probability of survival	16/24 Moderate
Coleman(309) UK 2001	2 887690	Head and neck cancer- larynx and oral cavity	**SES**- Carstairs index	1971- 1995	1 yr survival Men vs. Women Larynx 83% vs. 79% Oral cavity 72% vs. 74% 5yr survival Men vs. Women Larynx 63% vs. 57% Oral cavity 43% vs. 52% 5yr survival difference Affluent vs. Deprived Larynx 68.4% Gap-9.3% Oral cavity 53.9% Gap -11.6%	Not described	16/24 Moderate
Booth(426) Canada 2010	854	Laryngeal cancer	**SES**- Community median household income	1 January 2003- 31 October 2007	5yr OS (%) Q1=poorest Q1 59.0 (CI 53.3-64.2) Q2 54.0 (CI 47.8-59.8) Q3 60.4 (CI 53.4-66.7) Q4 56.8 (CI 48.5-64.4) Q5 60.0 (CI 52.2-66.9) P=0.045 3yr CSS (%) Q1 73.3 (CI67.1-78.5) Q2 65.3 (CI 58.0-71.6) Q3 80.4 (CI 74.3-85.2) Q4 75.3 (CI 67.0-81.8) Q5 75.8 (CI 68.0-81.9) P=0.011	Controlled for stage of disease at diagnosis and age	17/24 Moderate

Konski(368) USA 2003	1073	Squamous cell carcinoma of the head and neck	**SES**- Education	Not specified	Univariable 2 yr OS Education level (college/technical school vs. less than college) 61% vs. 46% p<0.0001 HR=1.46 Multivariable OS Education level (college/technical school vs. less than college) HR= 1.30 P=0.0056	Adjustment for education level, N classification, T classification, Karnofsky Performance Score (KPS), anatomic site, and race	16/24 Moderate
Puigpinos(369) Spain 2009	Exact numbers unknown, part of a larger cohort	Mouth, pharynx and larynx cancer	**SES**- Education level	1992- 2003	Relative index of inequality (RII)- ratio of death between death rates of the highest and lowest educational levels Larynx cancer Men vs. women 1992-94 2.82 1995-97 3.70 1998-2000 4.17 2001-03 3.23 Mouth and pharynx Men vs. Women 1992-94 3.37vs. 0.43 1995-97 4.85 vs. 1.74 1998-2000 2.24 vs. 1.43 2001-03 2.98 vs. 0.50	Not described	14/24 Moderate
Menvielle(371) France 2007	259 905	Upper aero-digestive tract cancer	**SES** by occupational class- Erikson, Goldthorpe, and Portecarero (EPG Score)	1968- 1974, 1975-1981, 1982- 1988, 1990-1996	RII 1968-74 All men 4.04 (CI 2.35, 6.93) Men in labour force 2.88(CI 1.58, 5.25) 1975-81 All men 10.76 (CI 6.66,17.4) Labour force 8.93 (CI 5.26,15.18) 1982-88 All men 11.06 (CI 7.26,16.87) Labour force 7.18 (CI 4.47,11.55) 1990-96 All men 18.75 (CI 11.23,31.30) Labour force 8.51 (CI 4.81,15.07)	Regression modelling of the 7 categories of EPG Score, and direct standardisation by age on mortality rates	15/24 Moderate
Chu (360) Canada 2011	2622	Oral cavity, oropharyngeal, larynx/hypopharynx and nasopharyngeal	**SES**- post code matching to 2006 Canada census tracts	2003- 2010	DSS Post secondary education p16-OPC HR 0.93 (CI 0.86, 0.99) p=0.03 Unemployment NPC HR 3.71 (CI 1.50, 9.51) p=0.01	Used multiple variable analysis adjusting for rural location, median income, nativity, transportation to work	17/24 Moderate

Anandan(354) Scotland 2008	556	Nasopharyngeal cancer	**SES**- Carstairs	1975-2001	Affluent vs. Deprived HR 0.57 (CI 0.41,0.79) p=.001 Log rank 15.32 df=4 p=.004	Adjustment for age, histological verification status, period of diagnosis, deprivation quintile, anatomical sub site.	13/24 Moderate
O'Hanlon(167) England 1997	Not specified	Oral cancer (tongue and mouth)	**SES**- Small area statistics	1975-1991	ASM Most deprived vs. Most affluent 1976-85 Tongue Males 134 vs. 69 Females 1986-1991 Mouth Males 142 vs. 61 Females 127 vs. 44 Mean SMR Northern region vs. England & Wales Tongue 148 vs. 106 Mouth 169 vs. 91	Not specified	13/24 Moderate
Edwards(355) England 1999	17 393	Upper aero digestive tract cancers	**SES**- Carstairs Index	1984-1993	5yr crude survival Quintile 1 48.4 (CI 47.7, 49.1) vs. Quintile 5 40.6 (CI 40.4,40.8) RR 1.6 (1.07, 1.26) Quintile 2/3 vs. 1.24 (CI 1.13,1.35) Quintile 4/5	Multivariate analysis by extent of spread, site and sub site, (mouth and pharynx)age, and deprivation	22/24 Strong
Groome(108) Canada 2006	661 glottic 495 supraglottic	Larynx, glottis, supraglottic and subglottic cancer	**SES**- Area level	1982-1995	RR affluent vs. Deprived 2.75 (CI 1.48, 5.12) CSS 1.90 (CI 1.24,2.93)	Adjusted for age,sex, rural residence, tumour stage, lymph node status, use of diagnostic imaging, treatment type	23/24 Strong
Robertson(358) Scotland 2010	1909	Head and neck cancer	**SES**- 2001 Depcat score	1 Sept 1999- 31 Aug 2001	Univariate HR (All cause mortality) Affluent 1.00 Intermediate 1.18 (CI 0.95,1.45) [0.91 (CI 0.64,1.29)] Deprived 1.33 (CI 1.06,1.68) [1.16 (CI 0.79, 1.70)] Multivariate HR Affluent 1.00 Intermediate 0.88 (CI 0.63, 1.22) [0.64 (CI 0.40, 1.00)] Deprived 0.93 (CI 0.64, 1.35) [0.82 (CI 0.49, 1.36)]	Adjusted stepwise for deprivation, WHO performance status, stage, site, age, smoking status, tumour differentiation, alcohol, sex.	21/24 Strong
Wong(372) Taiwan	1010	Oral cancer	**SES**- socio-demographic factors (occupation)	March 1995- December 2002	5yr OS 63.24% 5yr survival (%)	Adjusted for stage, age, gender, marital status	22/24 Strong

2006					Occupation log rank 10.74 p=0.005 None 58.30 Unskilled 70.57 Professional/managerial 65.60	and religious beliefs	
Warnakulasuriya(357) England 2007	5319	Oral cancer	**SES**- Indices of Deprivation	1986- 2002	OS- Univariate Age group 0-44yrs Affluent HR=1.00 Group 2 HR=1.19 (CI 0.62,2.27) Group 3 HR=1.16 (CI 0.62,2.17) Group 4 HR=1.53 (0.87, 2.71) Deprived HR=2.12 (CI 1.23,3.66) p<.002 Age group 45yrs and over Affluent HR=1.00 Group 2 HR=1.98 (CI 1.75,2.25) Group 3 HR=1.50 (CI 1.33,1.71) Group 4 HR=2.96 (CI 2.57, 3.41) Deprived HR=1.85 (CI 1.67,2.05) p<.001 OS multivariate Affluent HR= 1.00 Group 2 HR=1.92 (CI 1.69,2.19) Group 3 HR=2.10 (CI 1.84,2.40) Group 4 HR=3.15 (CI 2.72, 3.64) Deprived HR=1.72 (CI 1.53,1.92) p<.001	Factors adjusted were age, stage, year of diagnosis, type of surgery, any radiotherapy received, socioeconomic status and cancer network by residence	22/24 Strong
Boffetta(356) Italy 1997	272	Laryngeal cancer	**SES**- Occupation	January 1979- December 1982	Risk of death (HR) Unskilled worker 1.0 (reference) vs. Skilled worker professional 0.8 (CI 0.6-1.2) Non significant better prognosis for skilled workers/professionals	Models were adjusted for age, tumour site, T stage, N stage, education, birthplace, tobacco smoking and alcohol drinking	20/24 Strong
Mackillop(359) Canada 1997	357 530 but HNC cohort number not given	All invasive cancers- head and neck cancer only	**SES**- Linked census enumeration and postal code	1982- 1991	**Risk of death by income** ≤20k 1.47 (1.24-1.74) >20k≤30k 1.32 (1.14-1.53) >30k≤40k 1.22 (1.05-1.41) >40k≤50k 1.07 (0.92-1.26) >50k 1.0 (reference) **Overall risk of death with decreasing income** 1.1 (1.07-1.13) **All cause mortality and by income group**	Controlled for age, sex, year of diagnosis, and cancer catchment area	19/24 Strong

					≤20k 1.47 (1.12-1.72) >20k≤30k 1. 27 (1.06-1.53) >30k≤40k 1. 16 (0.96-1.39) >40k≤50k 1.01 (0.83-1.22) >50k 1.0 (reference) **Disease specific mortality by income** ≤20k 1.38 (1.24-1.74) >20k≤30k 1.32 (1.14-1.53) >30k≤40k 1.22 (1.05-1.41) >40k≤50k 1.07 (0.92-1.26) >50k 1.0 (reference)		
Kwok(367) USA 2010	1231	Head and neck cancer	**SES**- Health insurance status	January 1998- 12 October 2007	**OS all cause mortality** adjHR Private 1.00 Medicaid/Uninsured 1.50 (1.07-2.11) Medicare<65yrs 1.69 (1.16-2.48) Medicare >65yrs 1.22 (0.85-2.11) **Relapse free survival** adjHR Private 1.00 Medicaid/Uninsured 0.93 (0.65-1.35) Medicare<65yrs 1.19 (0.80-1.77) Medicare >65yrs 0.95 (0.65-1.77)	Controlled for age, gender, race, anatomic tumour site, treatment, stage at diagnosis, occupational prestige, alcohol and tobacco use	23/24 Strong
Rosso(370) Italy 1997	294	Mouth and pharynx cancer (as part of a variety of other cancers)	**SES**- Education level	1985- 1992	**Case fatality ratio (CFR)** Primary school 1.00(reference) Middle school 1.12 (0.78-1.62) High school 0.78 (0.39-1.55) University 0.70 (0.34-1.47) P=0.401	Adjusted for age, sex, area of birth, and housing tenure	18/24 Strong
Chu(364) USA 2011	53 544	Head and neck cancer	**SES**- Neighbourhood level SES	1 January 1988- 31 December 2007	Multivariable DSS Neighbourhood SES High SES (state-wide quintile 4-5) vs. Low SES (state-wide quintile 1-3) Oral 1.07 (CI 1.01-1.14) Oropharynx 1.34 (CI 1.25-1.43) Hypopharynx/Larynx 1.22 (CI 1.15-1.29) Nasopharynx 1.31 (CI 1.18-1.47) Asians and Pacific Islanders High vs. Low SES 1.26 (CI 1.08-1.48)	Controlled for age at diagnosis, sex, race/ethnicity, marital status, tumour stage, tumour histological grade, initial treatment modality, university teaching hospital	23/24 Strong

de Graeff(361) The Netherlands 2001	208	Head and neck cancer	**SES**- Family income	May 1994- June 1996	No statistically significant results found	Controlled for sex, age, marital status, family income, occupation, number of cigarettes smoked, units of alcohol consumed, KPS, site, AJCC stage, grade of differentiation, treatment, and radicality	22/24 Strong
Arbes(311) USA 1999	7503	Oral cancer	**SES**-Median household income	1988- 1993	Risk of death (unadjHR) ≥50k 1.00 (reference) 35-49k 1.1 (CI 1.0-1.3) 25-34k 1.3 (CI 1.1-1.4) ≤24k 1.6 (CI 1.4-1.8) Unknown 1.3 (CI 1.1-1.5) ≥50k 1.00 (reference) 35-49k 1.1 (CI 0.9-1.3) 25-34k 1.2 (CI 1.0-1.4) ≤24k 1.6 (CI 1.3-1.9) Unknown 1.4 (CI 1.1-1.7) Blacks vs. Whites (HR) (race, age, area and SES) All cause 1.4 (CI 1.2 - 1.5) Oral cancer 1.3 (CI 1.0-1.7)	Adjusted models for age, geographic area, race, anatomic site, year of diagnosis, grade, marital status, SES, lymph node, tumour size, treatment, and stage	23/24 Strong
McDonald(212) Canada 2014	Oropharynx 7022 Oral cavity 8541 Naso/hypo/laryngeal 14655	Oropharyngeal, oral cavity, hypopharyngeal, laryngeal and nasopharyngeal cancer	SES – Median household income	1991, 1996, 2001	2 yr OS Highest quintile is reference category Oropharynx 2nd OR 0.826 p=0.018 3rd OR 0.785 p=0.000 4th OR 0.691 p=0.000 5th OR 0.620 P=0.000 Oral cavity 2nd OR 0.892 P=0.271 3rd OR 0.885 p=0.137 4th OR 0.793 p=0.007 5th OR 0.675 p=0.000 Naso/hypo/laryngeal 2nd OR 0.863 p=0.008 3rd OR 0.806 p=0.001 4th OR 0.755 p=0.000	Not described	22/24

					5th OR 0.626 p=0.000		
Chang(210) Taiwan 2013	4691	Nasopharyngeal cancer	SES – Individual and Neighbourhood	2002-2007	5 yr OS Under 65 years Disadvantaged neighbourhood Low SES ref category Advantaged Low SES HR 0.91 Disadvantaged Moderate SES HR 0.77 Advantaged Moderate SES HR 0.71 Disadvantaged High SES HR 0.72 Advantaged High SES HR 0.54 5 yr OS Over 65 years Disadvantaged neighbourhood Low SES = Reference category Adv Low SES HR 0.88 Disadvantaged Moderate SES HR 0.81 Advantaged Moderate SES HR 0.87 Disadvantaged High SES HR 0.79 Advantaged Low SES HR 0.71	Adjusted for age, gender, geographic location, treatment modality, severity of disease, and monthly income	19/24
Lee (211) Taiwan 2012	3607	Oral cancer	SES – Individual and Neighbourhood	2004-2005	High SES HR= 1.46 Low SES HR= 1.64	Adjusted for age, gender, CCI, urbanization, and area of residence, tumor extent, treatment modalities (operation, adjuvant therapy), hospital characteristics (ownership, teaching level, caseload), and year of diagnosis	20/24
Reitzel (366) USA 2012	1784	Salivary gland, nasopharyngeal, or lip carcinoma,	SES – Neighbourhood level economic deprivation	February 1996-November 2009	Highly deprived relative to less deprived HR 1.59 (1.00–2.53) OS 2.91 (1.63–5.17), p=0.001 DSS 2.55 (1.24–5.27), p=0.011 DFS 1.95 (1.05–3.62) p=0.034	Adjusted for age, sex, race/ethnicity, income, smoking status, cancer site, cancer stage, and treatment approach	23/24

DFS – Disease free survival OS – Overall survival DSS- Disease specific survival CSS- Cancer specific survival

HR- Hazard ratio RR- Relative risk OR- Odds ratio CI- 95% confidence interval

unadjHR- Unadjusted hazard ratio adjHR- Adjusted hazard ratio

Appendix A9

Research & Development approval

NHS Tayside

11 December 2012

Ms Elsie Makachiya
PhD Student
University of Dundee
Population Health Sciences
Mackenzie Building
Kirsty Semple Way
DUNDEE
DD2 4BF

Dear Ms Makachiya,

R & D MANAGEMENT APPROVAL – TAYSIDE

Title: The effect of deprivation and comorbidity on head and neck cancer presentation and prognosis in the community.

Chief Investigator: Ms Elsie Makachiya

Principal Investigator/Local Collaborator: Ms Elsie Makachiya

Tayside Ref: 2012ON58 **NRS Ref: N/A**

REC Ref: N/A (Generic HIC Approval)

Sponsor: University of Dundee (Generic HIC Approval)

Funder: Unfunded

Many thanks for your application to carry out the above project here in NHS Tayside. I am pleased to confirm that the project documentation (as outlined below) has been reviewed, registered and Management Approval has been granted for the study to proceed locally in Tayside.

Approval is granted on the following conditions:-

- ALL Research must be carried out in compliance with the Research Governance Framework for Health & Community Care, Health & Safety Regulations, data protection principles, statutory legislation and in accordance with Good Clinical Practice (GCP).
- All amendments to be notified to TASC R & D Office.
- All local researchers must hold either a Substantive Contract, Honorary Research Contract, Honorary Clinical Contract or Letter of Access with NHS Tayside where required (http://www.nihr.ac.uk/systems/Pages/systems_research_passports.aspx).
- TASC R & D Office to be informed of change in Principal Investigator, Chief Investigator or any additional research personnel locally.
- Notification to TASC R & D Office of any change in funding.

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- As custodian of the information collated during this research project you are responsible for ensuring the security of all personal information collected in line with NHS Scotland IT Security Policies, until destruction of this data.

- All eligible studies will be added to the UKCRN Portfolio http://public.ukcrn.org.uk/. Recruitment figures for eligible studies must be recorded onto the Portfolio every month: This is the responsibility of the lead UK site. If you are the lead, or only, UK site, we can provide help or advice with this. For information, contact Charles Weller – (01382) 7 40128 – charles.weller@nhs.net or Liz Livingstone – (01382) 7 40126 – elivingstone@nhs.net.

- Annual reports are required to be submitted to TASC R & D Office with the first report due 12 months from date of issue of this management approval letter and at yearly intervals until completion of the study.

- Notification of early termination within 15 days or End of Trial within 90 days followed by End of Trial Report within 1 year to TASC R & D Office.

- You may be required to assist with and provide information in regard to audit and monitoring of study.

Please note you are required to adhere to the conditions, if not, NHS management approval may be withdrawn for the study.

Approved Documents

Document	Version	Date
Protocol		
Project Registration Form – Research Governance, Ethics and NHS Resources		

May I take this opportunity to wish you every success with your project.

Please do not hesitate to contact TASC R & D Office should you require further assistance.

Yours sincerely

Keith Gillon
Senior R&D Manager

TAyside medical **S**cience **C**entre (TASC)
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c.c. Dr Shaun Treweek
Mr Duncan Heather

Data Analysis Plan

Rationale: - This plan is intended to provide a comprehensive road map of the statistical methods that will be used to calculate the survival of HNC patients from datasets from 2006 onwards. The time period 2006 till present was chosen as this is the period from which records of all diagnosed cases of HNC in Fife and Tayside are available. These datasets will be assessed using comorbidity and SES as the explanatory variables for determining survival.

Objectives

- **Primary**

To determine the likelihood of survival for patients diagnosed with HNC dependent on their level of comorbidity (none, mild or severe) and SES (affluent or deprived).

- **Secondary**

To assess the survival of low SES (deprived) patients with comorbidity; and those without comorbidity vs. high SES (affluent) patients with and without comorbidity.

Outcome of interest

Death which can be described as:-

- All cause mortality
- HNC specific mortality
- Recurrence free survival

Definition of HNC- will be restricted to squamous cell carcinomas as this is the predominant type of HNC. Dependent on sub types, sub group analyses will be done e.g. laryngeal vs.

oropharyngeal while tonsil and oropharynx sub types will be explored as it has been suggested that these forms of HNC have the worst survival.

Hypothesis

Low SES alongside severe comorbidity equates to poor survival, i.e. the risk of death is increased in the presence of deprivation and severe comorbidity.

Factors to account for

Consider all cause mortality: The reasoning behind this approach is that prognosis is determined by other causes of death not just HNC, as death is dependent on patient characteristics such as age, gender, comorbidity, income, education, tumour stage etc.

Potential confounders:

- treatment type,
- duration of therapy (where applicable),
- ethnicity,
- tumour stage,
- anatomical subsite,
- age,
- sex,
- performance status,
- alcohol use,
- urban/rural residence,

- smoking status,
- hospital location/ teaching hospital status
- prior malignancies.

Data analysis methods: HNC patient datasets from Tayside and Fife

- SMR01- Morbidity records
- GRO Death records
- Scottish Cancer Registry data

Descriptive statistics

1. Frequencies of demographic information
2. Age, SES and gender distributions of cohort
3. Cross tabulations of comorbidity by age, HNC by diagnosis, cancer stage by comorbidity/ SES
4. Chi-square test to measure differences between groups

Survival analysis

1. Kaplan Meier survival analysis
2. Cox proportional hazards regression
3. Missing data analysis and imputation methods will be attempted

Explanatory variables of interest: The influence of comorbidity status and SES on survival will be examined using time to event data, i.e. survival analysis is the appropriate analysis. It is not limited to a date range therefore follow up of all patients should be possible.

Rationale: Model the underlying distribution of event times and to assess the dependence of the event time on other explanatory variables.

Approach

1. Construct Kaplan Meier survival curves to estimate distribution of survival times within the cohort.

2. Use life tables to calculate the cumulative survival probability and 95% confidence intervals.

3. Use Cox regression for assessing the relationship between survival times and the explanatory variables, comorbidity and SES (to model each variables contribution to the outcome of interest).

4. Comparison of 2 survival distributions Affluent vs. Deprived.

Presentation of analysis results

This will be done in narrative form in combination with graphics. Tables and figures will be used to heighten reader interest in the analysis and also to simplify the complex data generated.